Holmium:YAG laser enucleation of the prostate (HoLEP) for the treatment of benign prostatic hyperplasia

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This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Purpose of application

An application requesting Medical Benefits Schedule (MBS) listing of holmium:YAG laser enucleation of the prostate (HoLEP) with or without tissue morcellation for the treatment of benign prostatic hyperplasia (BPH) was received from MD Solutions Pty Ltd by the Department of Health and Ageing in May 2010.

A team from the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney was contracted to conduct a systematic review of the literature and an economic evaluation of the procedure in the treatment of BPH for MSAC consideration. A decision analytic protocol (DAP) was developed prior to the commencement of the assessment, and was approved by the Protocol Advisory Sub-Committee (PASC) of MSAC. The purpose of DAPs is to describe in detail a limited set of decision option(s) associated with the possible public funding of proposed new medical technologies and procedures. DAPs also accurately capture the current clinical practice and reflect the likely future practice with the proposed new medical technologies and procedures, and provide a description of all potentially impacted healthcare resources. The guiding framework of the DAP was used throughout this assessment.

Description of the proposed intervention

HoLEP is a relatively new surgical treatment option for men with BPH in whom surgery is indicated. Light from holmium:YAG lasers – which contain a crystal of yttrium, aluminium and garnet (YAG), doped with holmium – has a defined wavelength which can be used to produce unique effects on targeted tissue. In this instance, these lasers serve as a precise cutting instrument for the dissection of prostatic lobes into a number of sections. Dissected lobes are then pushed into the bladder, where they are cut into smaller pieces and removed– often using a morcellator.

This treatment is not currently in widespread use in Australia. It is known however that the procedure is available in some private hospitals through patient self-pay arrangements. It has been claimed that this new procedure, if more widely available, may confer some advantages over existing surgical options for men with BPH. It is claimed it may reduce the number of post-operative complications and reduce the risk of bleeding in some men (Tooher 2003). This would make it a more suitable alternative for those men with cardiovascular disease or those who are elderly and infirm. Moreover, it is claimed that this procedure could in some instances be performed as day surgery (Larner et al 2003).

Benign prostatic hyperplasia (BPH)

BPH is a non-malignant overgrowth of the prostate gland. BPH can arise as a result of physiological dysfunction or anatomical obstruction of the urinary tract (or a combination of these), and typically involves three factors:

- A histological change of hyperplasia within the gland
- Clinically determined enlargement of the prostate gland
- The clinical syndrome of lower urinary tract symptoms (LUTS).

Clinical BPH is very common in the ageing man and is most often associated with various LUTS which can cause urinary obstruction or irritation. Moderate to severe symptoms are recognised as significantly impacting on quality of life. The first-line management for men with BPH includes a variety of pharmaceuticals, including alpha receptor blockers, 5-alpha reductase inhibitors and anti-cholinergic drugs. These pharmaceuticals however have both high failure and high discontinuation rates (the latter due to side effects), and the BPH symptoms in the majority of men will progress. Many of these men will eventually undergo second-line surgical treatments. In addition, some men may not opt for initial medical management.

Transurethral resection of the prostate (TURP), MBS item number 37203, is considered the gold standard for the treatment of bladder obstruction for men with moderate prostate sizes estimated to be smaller than 80–100g. Open prostatectomy, MBS item number 37200 (or two-stage TURP), is considered the gold standard in men with larger prostates estimated at greater than 80–100g.

HoLEP is proposed as an alternative procedure to TURP for men with moderately sized prostates (estimated to be less than 80–100g). HoLEP is further proposed as an alternative to open prostatectomy in men with larger prostates (estimated to be more than 80–100g). In centres where it is available it would be expected to replace the alternative procedures listed above which have more recently been approved by MSAC.

There were 12,673 MBS claims for TURP procedures in the year 2010–2011. A much smaller number of claims during the same time period were recorded for open prostatectomy (OP) (141), transurethral needle ablation (TUNA) (4), transurethral microwave therapy (TUMT) (43) and visual laser ablation of the prostate (VLAP) (938).

Proposal for public funding

The proposed MBS item descriptor for HoLEP is:

Category 3 –THERAPEUTIC PROCEDURES
MBS [item number] Endoscopic enucleation of the prostate using high powered (>= 100W) laser and an end-firing, non-contact fibre with or without tissue morcellation (Anaes)
Fee: $1423.18

The item descriptor included in the final DAP proposed that HoLEP would be employed with tissue morcellation, that is 'Endoscopic enucleation of the prostate using high powered (>= 100W) laser and an end-firing, non-contact fibre with tissue morcellation (Anaes)'. It was noted by the Protocol Advisory Sub-Committee (PASC) of

MSAC however that morcellation does not occur in every case, and this could lead to compliance issues if the prescriptive wording 'with tissue morcellation' were retained. The alternate descriptor –'with or without tissue morcellation' – is provided instead.

HoLEP is not expected to completely replace TURP or OP, but may be offered as an alternative to some men in those centres where it is available.

There is a learning curve to develop skills in HoLEP which would require considerable investment from urologists in terms of both time and money. Due to the high level of specialisation and skills required, the procedure would be performed by urologists whose main focus of practice is treating prostate conditions and who had undertaken the appropriate training. HoLEP would therefore be undertaken in specialist urology centres by specially trained urologists.

Current arrangements for public reimbursement

Other surgical interventions for BPH have been assessed by MSAC in the past. These include TUNA for benign prostatic hyperplasia (MSAC report 1014, MBS item 37201) and high-energy TUMT (MBS 37230) for benign prostatic hyperplasia (MSAC report 1076). VLAP(MBS item 37207) has also been included on the MBS since July 1995 (which pre-dates the MSAC).

Prerequisites to implementation of any funding advice

Twelve holmium:YAG lasers are currently TGA-registered and listed on the Australian Register of Therapeutic Goods (ARTG). Three tissue morcellators are also TGA-registered and listed on the ARTG.

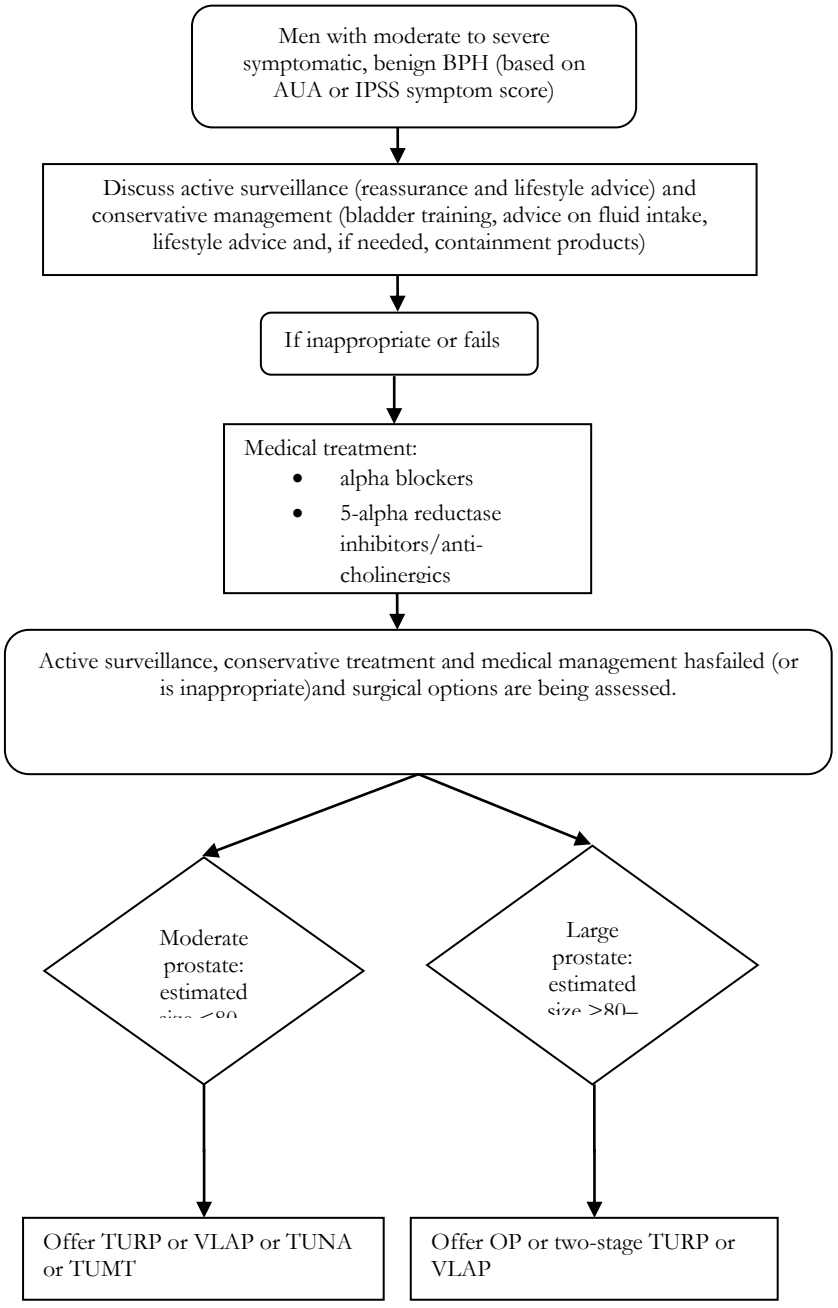
Consumer Impact Statement

Public comment was sought during the development of the final DAP. The DAP was released for public comment on 24 February 2011 and closed for comments on 31 March 2011. This public comment was incorporated into the final DAP as a result of PASC deliberation on 13–14 April 2011.

Clinical need

The current management algorithm for men with moderate to severe BPH (as defined by the American Urological Association – AUA- or International Prostate Symptom Score – IPSS) is depicted in Figure 1 below.

Figure 1: Current clinical management chart for patients with BPH



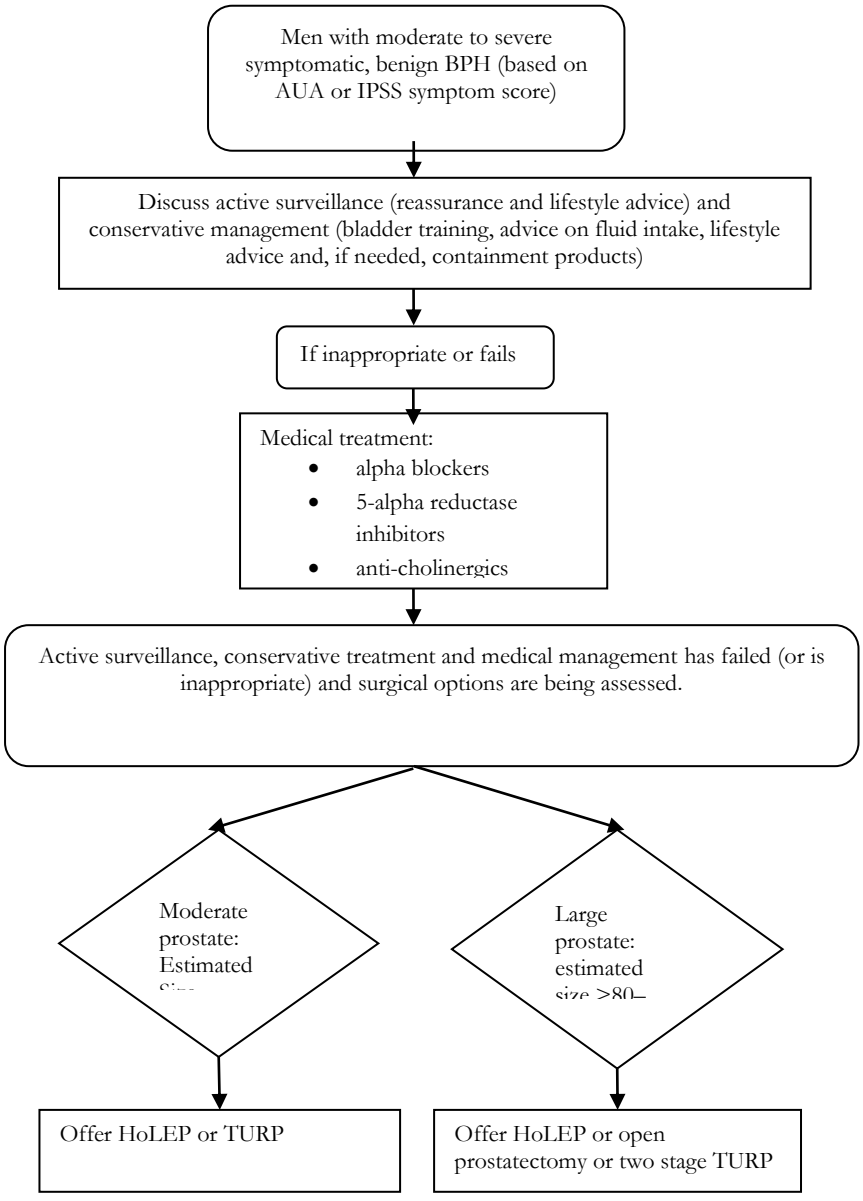
There are therefore two groups of men for whom a surgical intervention for the treatment of BPH would be indicated. These are:

- Men with moderate-sized prostates (estimated at less than 80–100g) – in this group, TURP would be considered the gold standard surgical treatment. Other surgical options are currently available for this group, including VLAP, TUNA or TUMT.

- Men with large prostate size (estimated at greater than 80–100g) – in this group, OP would be considered the gold standard. Other alternatives that are considered appropriate and currently available include a two-stage TURP procedure or VLAP

It was proposed in the application that HoLEP (where it is available) could be used as an alternative to existing surgical procedures in each of the groups listed above. This is depicted in Figure 2 below.

Figure 2: Proposed management using HoLEP



Comparator to the proposed intervention

Although a number of surgical options are available for men with moderate-sized prostates (less than 80–100g), only TURP was considered a suitable comparator for HoLEP in this evaluation. For men with larger prostates (greater than 80–100g), OP was the comparator that was used for assessing the evidence for HoLEP.

The newer surgical interventions for BPH (that is, TUNA, TUMT and VLAP) were not considered suitable comparators. This is because they have lower utilisation rates and represent smaller costs to the MBS relative to the gold standards. Furthermore, if approved, HoLEP would be expected to replace these procedures in centres where it would be available. This approach, described in the DAP was agreed to by PASC.

TURP accounts for the vast majority of surgical procedures for BPH. Under general, epidural or spinal anaesthesia, a small electric loop is introduced into the urethra via a rectoscope. Slivers of excess tissue are excised and then electrical current is applied to cauterise the wound.

Complications can include bleeding that may require transfusion, acute urinary retention, infections and urethral stricture. A very rare and serious complication known as 'TUR syndrome' (dilutional hyponatraemia) can also occur, although it is treatable. Larger prostates are considered poor candidates for TURP, in part due to longer resection times leading to higher complication rates. Resection time can be limited to avoid complications with patients returning for a second TURP if further resection is required.

An indwelling catheter is usually required for 12 to 24 hours as is a hospital stay of one to three days. TURP requires full operating room facilities and utilises equipment such as a standard diathermy generator with cutting and coagulation outputs and standard video-endoscopic equipment.

The procedure is performed by an urologist with the assistance of nursing staff and an anaesthetist. Standard inpatient pathways requiring ward and recovery staff also apply.

The MBS item descriptors for TURP are:

Category 3 – THERAPUTIC PROCEDURES
MBS 37203 PROSTATECTOMY (endoscopic, using diathermy or cold punch), with or without cystoscopy and with or without urethroscopy, and including services to which item 36854, 37201, 37202, 37207, 37208, 37303, 37321 or 37324 applies (Anaes.) Fee: $1,002.70 Benefit: 75% = $752.00

Category 3 – THERAPUTIC PROCEDURES
MBS 37206 PROSTATECTOMY (endoscopic, using diathermy or cold punch), with or without cystoscopy and with or without urethroscopy, and including services to which item 36854, 37303, 37321 or 37324 applies, continuation of, within 10 days of the procedure described by item 37201, 37203 or 37207 or which had to be discontinued for medical reasons (Anaes.) Fee: $536.95 Benefit: 75% = $402.75

OP is performed in men with large prostates or those for whom hip or other medical conditions preclude the physical positioning required for TURP. OP is performed through a lower abdominal incision, and either through the bladder or through the capsule of the prostate. It involves a longer hospital stay and increased risk of bleeding in comparison to TURP. It does however have lower re-treatment rates and no risk of TUR. A general or spinal anaesthetic is required.

The MBS item descriptor for OP is:

Category 3 – THERAPUTIC PROCEDURES
MBS 37200 PROSTATECTOMY, open (Anaes.) (Assist.) Fee: $977.80 Benefit: 75% = $733.35

Scientific basis of comparison

Searches of literature databases as well as health technology assessment (HTA) websites yielded nine HTAs and systematic reviews that compared HoLEP with TURP and OP. Four of these systematic reviews and HTAs compared HoLEP with TURP, and five compared HoLEP with TURP and OP.

The report of Lourenco et al (2008), providing a direct comparison of HoLEP with TURP in men with BPH, was chosen by the evaluation group for updating. This is a high-quality systematic review, developed as part of the UK National Institute for Health (NIHR) Research Health Technology Assessment programme, which had the objective of determining the clinical and cost-effectiveness of surgical treatment alternatives to TURP. This review identified five randomised controlled trials (RCTs) from which data on comparative safety and effectiveness were extracted and analysed by the authors.

A systematic review undertaken by the Australian and New Zealand Horizon Scanning Network (ANZHSN) was chosen for updating in the evaluation of HoLEP versus OP. Two RCTs (four publications) were reported on in this review. Three other non-randomised comparative studies were also reported. These however did not meet the inclusion criteria.

Five further RCTs comparing HoLEP with TURP that were published subsequent to the Lourenco et al systematic review (2008) were identified by the evaluation group. Three of these were follow-up reports of existing studies that had been included in the systematic review, and two were more recently published studies that would not have been included.

No additional studies comparing HoLEP with OP were identified. The RCTs reported on in the ANZHSN therefore comprise the evidence base for the comparative safety and effectiveness of these interventions.

In comparing safety and effectiveness outcomes for HoLEP versus TURP, meta-analysis of data from the studies identified in the Lourenco et al report (2008) together with data from the two more recent studies was undertaken where appropriate. Meta-analysed results from the Lourenco study are reported for some outcomes when no additional data were extracted from the newer studies. Narrative description of some outcomes is provided when meta-analysis of the data was not possible.

In comparing HoLEP with OP, meta-analysis of data from the two RCTs identified in the ANZHSN report was undertaken where feasible. Narrative description of other outcomes is provided when meta-analysis of the data was not possible.

Comparative safety

Key results of safety comparison of HoLEP with TURP

A summary of the main results of the comparison are shown in Table 1 below.

Table 1: Safety of HoLEP compared with TURP

Outcome	Studies (n)	Patients HoLEP /TURP (n)	HoLEP (total events)	TURP (total events)	Estimate of effect	Range (95% CI)*	I2 (%)	p-value
Blood transfusion rates	7	348/342	1	13	RR 0.27	0.09–0.85	0	0.02
Urethral stricture	7	322/309	14	23	RR 0.65	0.33-1.27	0	0.21
Incontinence	6	306/296	7	8	RR 0.84	0.31–2.28	0	0.97
Acute urinary retention*	5	293/287	15	21	RR 0.71	0.38–1.32	8	0.28
Urinary tract infection*	2	91/89	5	5	RR 0.98	0.31–3.09	37	0.97

RR= relative risk; * Results are from Lourenco et al (2008) as no additional data were reported in the more recent studies.

It was not possible to meta-analyse data for a number of other safety outcomes listed in the DAP, including dysuria, TUR syndrome, erectile dysfunction and overall mortality. Individual studies did include these, although statistically significant differences between the two interventions were not reported.

Key results of safety comparison of HoLEP with OP

A summary of the main results are shown in Table 2 below.

Table 2: Safety of HoLEP compared with OP

Outcome	Studies (n)	Patients HoLEP /OP (n)	HoLEP (total events)	OP (total events)	Estimate of effect (RR)	Range (95% CI)*	I2 (%)	p-value
Blood transfusion rates	2	101/99	2	15	0.19	0.05–0.73	0	p=0.02
Urethral stricture	2	101/88	5	4	1.12	0.31–4.06	0	p=0.87
Incontinence	2	97/99	7	9	0.79	0.31–2.04	0	p=0.63

RR= relative risk.

A number of other outcomes, listed in the DAP, were reported on in either of the studies and were not meta-analysed. These include erectile dysfunction, acute urinary retention and dysuria. Statistically significant differences were not reported between the interventions.

Key uncertainties

Areas of uncertainty can arise in the interpretation of safety outcomes that are extracted only from RCTs. Less frequently observed complications that may be reported in large

cohort studies may not be identified. It is possible therefore that different estimates of safety may be obtained by reviewing data from non-randomised or cohort studies. Longer term, or less frequently observed, complications also may not be reported in short term trials. In this assessment, follow-up data published subsequent to the original RCTs does however provide more robust estimates of complications.

Surgeon experience was also not noted in the majority of the studies. It is possible that complication rates that would be observed in current clinical practice may be different.

The time point of recording of some of the adverse events (urinary stricture and urinary incontinence) was not specified. The Lourenco et al report for example notes that these complications could not be separated into those reported in the immediate postoperative period and those experienced over the course of the trials. These adverse events were pooled together in this assessment despite this limitation. The results reported should be interpreted within this context.

Overall conclusion with respect to comparative safety

HoLEP appears to be as safe as TURP across the range of outcomes assessed. There would appear to be statistically significant advantages over TURP in relation to blood transfusion rates post procedure. The evidence from the systematic review and two additional RCTs suggests that differences in the rates of other adverse events are not statistically significant. Some caution should be exercised in the interpretation of this information given the wide confidence intervals that exist around some of the outcomes.

HoLEP also appears to be as safe as OP across the range of outcomes assessed, although this information is analysed from fewer studies and with a smaller number of patients. In a meta-analysis of the two studies, patients allocated to HoLEP were less likely to have a blood transfusion that than those allocated to TURP. Other complications, such as incontinence and stricture, were comparable between the groups.

Comparative effectiveness

Key results of effectiveness comparison of HoLEP with TURP

Evidence informing an assessment of the comparative effectiveness of the two interventions was obtained from the same systematic searches described above. A summary of the main results are shown in

Table 3 below.

Table 3: Effectiveness of HoLEP compared with TURP

Outcome	Studies (n)	Patients HoLEP /TURP (n)	HoLEP (mean)	TURP (mean)	Estimate of effect (MD)	Range (95% CI)*	I^2 (%)	p-value
Qmax @ 6 months(ml/s)	6	323/315	24.2	23.3	0.99	-0.81–2.80	62	0.28
Qmax @ 12 months(ml/s)	6	317/310	25.0	23.4	1.39	0.64–2.15	9	0.002
Qmax @ 24 months (ml/s)	3	147/142	24.7	23.1	1.14	-2.17–4.46	41	0.5
IPSS/AUA @ 6 months (score)	6	323/315	4.0	4.4	-0.66	-1.34–-0.03	71	0.06
IPSS/AUA @ 12 months (score)	6	295/296	3.6	4.4	-0.96	-1.73–-0.18	80	0.02
IPSS/AUA @ 24 months (score)	2	125/116	2.6	3.8	-1.49	-3.29–0.32	63	0.11
PVR volume @ 6 months (mls)	3	160/158	14.7	28.7	-11.9	-14.74–-9.17	0	<0.001
PVR volume @ 12 months (mls)	2	129/126	5.3	25.4	-19.4	-25.55–-13.16	0	< 0.001
Treatment failure/re-treatment**	2	91/89	1**	5**	RR 0.27	0.04–1.60	0	0.15
Quality of life @ 6 months*	3	139/136	1.2	1.2	0.25	0.05–0.44	77.3	0.01
Quality of life @ 12 months*	3	138/134	1.3	1.3	0.06	-0.26–0.38	86.2	0.73
Quality of life @ 24 months*	2	67/67	1.1	1.1	-0.01	-0.40–0.38	0	0.96

Qmax = peak flow; PVR = post-void residual volume; MD = mean difference; RR = relative risk; * Results are from Lourenco et al (2008) as no additional data were reported in the more recent studies; ** Total number of events, rather than mean.

Some statistically significant differences between HoLEP and TURP are demonstrated from this data, including Qmax (peak flow) at 12 months, symptom scores at 6 and 12 months as well as post-void residual volume (PVR). Caution should be exercised in interpreting these results however due to the wide confidence bounds and significant heterogeneity across the studies.

No significant differences were reported in respect to treatment failure or re-operation rates. Pooled quality of life results from the Lourenco et al systematic review indicate that there are no significant differences between the interventions at 12 and 24 months. Longer term follow-up recently published also shows no significant differences. It was not possible to pool results for prostate volume.

Bother scores were included in the DAP as an effectiveness outcome to be assessed. However, none of the studies included in this review reported on this outcome.

A number of secondary effectiveness outcomes including duration of procedure, duration of catheterisation and duration of hospital stay were also analysed in this review. These are summarised in Table 4 below.

Table 4: Secondary effectiveness outcomes: HoLEP compared with TURP

Outcome	Studies (n)	Patients HoLEP /TURP (n)	HoLEP (mean)	TURP (mean)	Estimate of effect (MD)	Range (95% CI)*	I2 (%)	p-value
Duration of operation (min)	6	331/336	70	54.6	15.8	8.70–21.46	72	p<0.00001
Duration of catheterisation (hours)	6	285/282	31.1	53.4	22.39	28.18–16.60	80	p<0.00001
Duration of hospital stay (days)	5	281/276	1.9	3.0	1.08	1.26–0.89	28	p<0.00001

MD=mean difference.

Key results of effectiveness comparison of HoLEP with OP

A summary of the main results are shown in Table 5 below.

Table 5: Effectiveness of HoLEP compared with OP

Outcome	Studies (n)	Patients HoLEP /OP (n)	HoLEP (mean)	OP (mean)	Estimate of effect (MD)	Range (95% CI)*	I^2 (%)	p-value
Qmax @ 12 months(ml/s)	2	93/84	24.9	26.3	1.53	3.51–0.45	0	p=0.13
Qmax @ 24 months (ml/s)	2	88/79	23.0	23.8	0.78	3.10–1.54	0	p=0.51
IPSS/AUA @ 12 months (score)	2	93/84	5.4	5.4	0.01	0.79–0.81	0	p=0.99
IPSS/AUA @ 24 months (score)	2	88/79	5.1	5.3	0.11	0.98–0.76	0	p=0.80
Treatment failure/re-operation	2	97/95	5*	6*	RR 0.82	0.26–2.59	0	P=0.73

MD= mean difference; RR = relative risk; * total number of events rather than mean.

Statistically significant differences associated with either intervention were not demonstrated at any time period in any of the three outcomes listed above.

Other outcomes listed in the DAP were included in either of the RCTs identified. These include PVR, prostate volume and quality of life scores. No statistically significant differences between the interventions were reported. Bother scores were listed in the DAP as an effectiveness outcome. These however were not reported in either study.

A number of secondary effectiveness outcomes including duration of procedure, duration of catheterisation and duration of hospital stay were also analysed in this review. None of the studies included reported on training, equipment or staffing costs. Both studies reported on length of operation, catheterisation and hospital stay. Due to the clinical heterogeneity of these studies in terms of the intervention, results were not pooled. A HoLEP procedure may take longer to complete than an OP procedure. It may be associated with a shorter hospital stay and shorter catheterisation times. These data must however be interpreted with caution.

Key uncertainties

There are wide confidence intervals across the reported results. Where statistically significant differences between the interventions occur, these differences may be small and may not be clinically relevant. Pooling of results indicates significant heterogeneity across the studies, particularly in relation to symptom scores and quality of life measures. This could, in part, be explained the lack of blinding in the trials.

Surgeon experience was often not noted in the studies. As HoLEP requires highly specialised skills it is possible that data on operative time and catheterisation may be an overestimate.

Overall conclusion with respect to comparative effectiveness

HoLEP appears to be as effective, or more effective, than TURP across a range of effectiveness outcomes. These include peak flow (Qmax), symptom scores PVR. Caution should however be exercised in the interpretation of these findings given wide confidence intervals and significant heterogeneity across the studies. Quality of life differences and differences between the two interventions in respect of treatment failure/re-treatment rates were not significant.

A HoLEP procedure takes longer to complete than a TURP procedure, but is associated with a statistically significant shorter hospital stay. Catheterisation times are also shorter. Surgeon experience was often not noted in the studies and so it difficult to ascertain whether these results would reflect current operative times. There is also significant heterogeneity across studies that assessed duration of operation and duration of catheterisation.

Based on the evidence from these two randomised controlled trials, HoLEP appears to be as effective as OP across a range of effectiveness outcomes. These include Qmax, symptom scores and PVRs. No evidence of superiority for HoLEP (or OP) was demonstrated in either of the studies.

A HoLEP procedure may take longer to complete than an OP procedure, but may be associated with a shorter hospital stay and shorter catheterisation times. These data must, as noted above, be interpreted with caution.

Economic evaluation

A cost utility analysis was undertaken that examined the costs and benefits of a number of surgical treatment strategies for BPH that included either HoLEP and/or TURP for men with prostate sizes of less than 80-100g or HoLEP and/or OP for men with larger prostates.

A Markov model was developed, allowing patients transition through health states over a time horizon of five years. Individual cycle lengths were six months with half-cycle correction employed to account for the continuous nature of transition probabilities within a cycle. Five years was chosen based on the availability of clinical effectiveness data used in the meta-analysis. In accordance with the DAP, patients who failed an initial HoLEP procedure could be re-treated with either HoLEP or TURP. Patients who failed a TURP procedure would be re-treated with TURP. In the OP comparison, patients who failed an initial HoLEP could be re-treated with either HoLEP or OP. There was no treatment alternative to a failed OP.

The model included health states of: initial treatment (with or without adverse events); well; long-term side effects; treatment failure; repeat treatment (with or without adverse events); treatment for urethral stricture; and death (all cause mortality). The transition through these health states was determined from the result of the literature review and meta-analysis.

Costs of TURP and OP procedures were taken from the private hospital weighted AR-DRG costs (with or without complications). Costs for HoLEP procedures were derived based on the TURP AR-DRG codes and also incorporating the additional MBS fees that were proposed with a reduced length of hospital stay.

In both economic evaluations HoLEP treatment was demonstrated to be associated with lower average per-patient treatment costs than treatment options including either TURP or OP, with equivalent or near equivalent effectiveness. This lower cost was driven by the reduced length of stay required for HoLEP treatment, as well as reduced rates of adverse events, long-term incontinence and treatment failure.

In the base case analysis, there was a marginal increase in effectiveness for TURP (with repeat TURP upon failure) of 0.008 QALYs. This was considered to be an artefact of the calculation of patient progression through the model, and the two treatments could be considered equally effective. The incremental cost-effectiveness ratio of HoLEP (with HoLEP up failure) was modelled to be $179,725/QALY over TURP (with TURP upon failure). The high ICER value is driven by the marginal difference in effectiveness between the treatment options. Overall, HoLEP treatment is associated with lower average per-patient costs with near equivalent effectiveness.

HoLEP treatment pathways were marginally more effective than those employing OP with a marginal increase of ~0.006 QALYs compared to OP treatment alone. HoLEP treatment (with either HoLEP or OP upon treatment failure dominated OP treatment in that they were less costly and more effective.

Treatment pathways that included HoLEP remained cost-effective against either TURP or OP across a range of variables tested in sensitivity analysis. TURP (with TURP for re-treatment) was more cost-effective than HoLEP in one scenario only. This was with an increased cost of HoLEP associated with a longer length of stay coupled with the highest confidence interval relative risk of HoLEP re-treatment for failure.

A number of potential MBS fees were listed in the DAP. The maximum of these fees was used in the base case. Reducing the fee from this rendered the treatment more cost-effective.

Overall conclusion with respect to comparative cost-effectiveness

HoLEP is considered to be a highly cost-effective alternative to either TURP or OP in the surgical management of men with BPH. This is primarily due to the reduced costs that are associated with the procedure, in turn driven by reduced lengths of stay in hospital and reduced complications. Scenarios that would reduce the cost-effectiveness of the procedure would include increased lengths of hospital stay or increased rates of re-operations required for the re-treating BPH.

Financial/budgetary impacts

There is a learning curve to develop skills in the procedure. It is likely therefore that uptake of the procedure following positive listing would initially be slow, and increase gradually over time. It is assumed in this assessment that by year 3 the uptake would be equivalent to 5% of the total number of TURP procedures that are undertaken annually; by year 5 the corresponding figure would be 10%. These assumptions would project that by year 3 there would be 625 procedures performed annually, rising to 1250 by year 5.

The listing of HoLEP would have an additional direct cost to the MBS on an annual basis as a result of the increased fee for the item. The indirect cost savings that occur – through reduced length of stay and reduced complications – would accrue to hospitals, to health insurers and to patients.

Based on the projections outlined in this assessment, it is estimated that the additional cost to the MBS as a result of positive listing of this procedure would be $201,465 by year 3 and rising to $398,589 by year 5. These costs reflect only the 75% Medicare benefit for the item and it is expected that any additional costs would be out-of-pocket.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of holmium:YAG laser enucleation of the prostate (HoLEP) (with or without tissue morcellation), a therapeutic intervention for the treatment of benign prostatic hyperplasia. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as: diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report for MSAC consideration, summarises the assessment by the NHMRC Clinical Trials Centre of the available clinical evidence at the time of the assessment for HoLEP, with or without tissue morcellation, for the treatment of benign prostatic hyperplasia (BPH).

Background

Holmium: YAG laser enucleation of the prostate

Holmium: YAG lasers contain an active medium of yttrium, aluminium and garnet (YAG), doped with holmium. The crystals from this combination are used to produce laser light which has a defined wavelength (2140nm) and can produce unique effects upon targeted tissue due to the particular absorption co-efficient produced by the wavelength. Holmium:YAG lasers can be used in several different surgical applications. Low-powered holmium:YAG lasers (5W to 30W), for example, are used for endoscopic destruction of stones occurring in the bladder or ureter. The holmium:YAG lasers used for cutting soft tissue such as prostatic adenoma are generally considered 'high-powered', that is capable of delivering 100W of power. End-firing lasers (as opposed to side-firing) allow for more precise thermal ablation of the tissue and hence more accurate cutting (Tooher 2003)

The term 'HoLEP' refers to holmium:YAG laser enucleation of the prostate, using high powered lasers that are end-firing. During the HoLEP procedure, the holmium laser is used to dissect the median and lateral lobes of the prostatic capsule. The procedure can be used to efficiently enucleate both small and large prostate glands. It is performed using a continuous flow rectoscope with a video system, and saline irrigation to maintain a clear view. Tissue necrosis is minimal, and the procedure is considered to be relatively bloodless. Once the tissue is enucleated, a tissue morcellator may be applied either trans-urethrally or supra-pubically, in order to aspirate the enucleated tissue from the bladder (Gilling & Fraundorfer 1998).

An application requesting MBS listing of HoLEP (with tissue morcellation) for the treatment of BPH was received from MD Solutions Pty Ltd by the Department of Health and Ageing in May 2010.A team from National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney was engaged to conduct a systematic review of safety, effectiveness and cost-effectiveness of this procedure in the treatment of BPH in order to inform a decision as to whether it should be listed.

The proposed MBS listing is:

Category 3 –THERAPEUTIC PROCEDURES
MBS [item number] Endoscopic enucleation of the prostate using high powered (>= 100W) laser and an end-firing, non-contact fibre with or without tissue morcellation (Anaes)
Fee: $1423.18

A decision analytic protocol (DAP) was developed prior to the commencement of the assessment, and was approved by the Protocol Advisory Sub-Committee of MSAC (MSAC 2011). The purpose of a DAP is to describe in detail a limited set of decision option(s) associated with the possible public funding of a proposed new medical service. ADAP also captures the current clinical practice and reflects the likely future practice

with the proposed new medical service, and describes all potentially impacted healthcare resources. The guiding framework of the DAP has been used throughout this assessment.

The item descriptor included in the final DAP proposes that HoLEP would be employed with tissue morcellation, that is 'Endoscopic enucleation of the prostate using high powered (>= 100W) laser and an end-firing, non-contact fibre with tissue morcellation (Anaes)'. It was noted by the Protocol Advisory Sub-Committee (PASC) of MSAC however that morcellation does not occur in every case, and this could lead to compliance issues if the prescriptive wording 'with tissue morcellation' were retained. The alternate descriptor –'with or without tissue morcellation' – is provided instead.

Intended purpose

HoLEP (with or without tissue morcellation) is intended to be used as an option for men with benign prostatic hyperplasia (BPH) for whom surgery is indicated. Surgery is usually considered as a second-line option in these patients, and a number of procedures are available. HoLEP may offer clinical advantages over these. In some men, it is claimed, it may reduce the number of post-operative complications and reduce the risk of bleeding (Tooher 2003). This would make it a more suitable alternative for those men with cardiovascular disease, those on anti-coagulants or those who are elderly and infirm.(Larner et al 2003).

Benign prostatic hyperplasia

BPH is a non-malignant overgrowth of the prostate gland. This overgrowth is experienced to some degree by the majority of men over 50 years of age. BPH can arise as a result of physiological dysfunction or anatomical obstruction of the urinary tract (or a combination of these factors), and typically involves:

- a histological change of hyperplasia within the gland
- a clinically determined enlargement of the prostate gland
- the clinical syndrome of lower urinary tract symptoms (LUTS).

Clinical BPH is very common in the ageing man and is most often associated with various LUTS which can cause urinary obstruction or irritation. Moderate to severe symptoms significantly impact on quality of life. The first-line management for men with BPH includes a variety of pharmaceuticals, including alpha receptor blockers, 5-alpha reductase inhibitors and anti-cholinergic drugs. However, these pharmaceuticals have both high failure and high discontinuation rates (the latter due to side effects), and the BPH symptoms in the majority of men will progress. Many of these men will eventually undergo second-line surgical treatments. In addition, some men may not opt for initial pharmaceutical management (Gallegos & Frazee 2008).

Transurethral resection of the prostate (TURP), MBS item number 37203, is considered the gold standard for the treatment of bladder obstruction for men with moderate prostate sizes, estimated to be less than 80–100g. Open prostatectomy (OP) or two-stage TURP, MBS item 37200, is considered the gold standard in men with larger prostates,

estimated at greater than 80–100 g. Other surgical interventions for BPH have been previously assessed by MSAC and recommended for public funding. These include transurethral needle ablation (TUNA) for benign prostatic hyperplasia (MSAC report 1014, MBS item 37201) and high-energy transurethral microwave therapy (TUMT) for benign prostatic hyperplasia (MSAC report 1076, MBS item 37230). Visual laser ablation of the prostate (VLAP), MBS items 32707 and 32708 has been MBS-listed since July 1995.

The number of men who undergo treatment for BPH annually in Australia can be estimated from the AIHW National Hospital Morbidity Database using the ICD-10-AM classification for separations shown in Table 6.

Table 6: Separations for principal diagnosis of BPH 1998-2010

	Year											
	98–99	**99–00**	**00–01**	**01–02**	**02–03**	**03–04**	**04–05**	**05–06**	**06–07**	**07–08**	**08–09**	**09–10**
N40 Hyperplasia of prostate Hospital separations	20,907	20,998	21,476	21,552	21,449	22,552	23,721	25,243	25,226	25,252	25,055	24,536

Source: AIHW National Hospital Morbidity Database.

The total number of Medicare items processed between July 2007 and June 2011 is shown in Table 7**Error! Reference source not found.**, and illustrate the casemix and osts to the Government of the different surgical procedures that may be used to treat the condition.

Table 7: Requested Medicare items processed from July 2007 to June 2011

MBS item number	Procedure	Fee	2007–08	2008–09	2009–10	2010–11
37203	Transurethral resection of prostate [TURP]	$1,022.70	12,158	12,557	12,690	12,673
37207	Visual laser ablation (VLAP)	$850.30	319	460	699	938
37224	Diathermy or visual laser destruction	$317.15	240	249	232	269
37200	Open prostatectomy	$997.35	141	153	142	141
37206	Transurethral resection of prostate [TURP] (continuation within 10 days)	$547.70	24	30	33	25
37230	Transurethral microwave thermotherapy [TUMT]	$1,022.70	59	62	28	43
37201	Transurethral needle ablation [TUNA]	$813.40	37	17	13	4
37208	Visual laser ablation (continuation within 10 days)	$408.30	2	2	2	1
37202	Transurethral needle ablation [TUNA] (continuation within 10 days)	$408.30	3	1	1	0
37233	Transurethral microwave thermotherapy [TUMT] (continuation within 10 days)	$547.70	1	0	1	0

Source: Medicare Australia statistics.

In this report HoLEP is evaluated as an alternative procedure to TURP for men with moderately sized prostates (estimated to be less than 80–100g).It is also evaluated as an alternative procedure to OP in men with larger estimated prostate sizes (greater than 80–100 g).

Existing procedures

Alternate treatments

Two alternate surgical options for the surgical treatment of BPH are in widespread use. These are: transurethral resection of the prostate (TURP) and open prostatectomy (OP). These are MBS listed.

Transurethral resection of the prostate (TURP)

TURP has traditionally been considered the surgical 'gold standard'(Gordon et al 1997). In Australia, TURP is the most frequently used surgical procedure for BPH, representing the highest cost to the MBS for treatment of this patient group. In 2010–11 for example, the total cost of TURP to the MBS (including MBS items 37203 and 37206 – see Table 7 above) amounted to $12.97 million.

During the TURP procedure, a small electric loop is introduced into the urethra via a rectoscope (while under general, epidural or spinal anaesthesia). Slivers of excess tissue are excised using the loop, and the electrical current is applied to cauterise the wound (Tooher 2003)(Tooher 2003).

TURP is indicated for patients with moderately sized prostates (estimated size less than 80–100g). Patients with larger prostate sizes are considered poor candidates for TURP. This is in part due to longer resection times, which can lead to higher complication rates. Resection time can be limited during the procedure so as to avoid complications, with patients returning for a second TURP if further resection is required. An indwelling catheter is usually required (for 12 to 24 hours) following the procedure, as is a hospital stay of one to three days. The procedure is performed by an urologist with the assistance of nursing staff and an anaesthetist. TURP requires full operating room facilities and utilises equipment such as a standard diathermy generator with cutting and coagulation outputs and standard video-endoscopic equipment.

Complications of the procedure can include bleeding(requiring blood transfusion), acute urinary retention, infections and urethral stricture. Less frequently, a "TUR syndrome" may also occur. This is where intravascular absorption of the irrigant used during the surgery causing dilutional hyponatraemia leads to agitation, confusion, and potentially seizure and coma.

The current MBS item descriptors for TURP are:

Category 3 – THERAPUTIC PROCEDURES
MBS 37203 PROSTATECTOMY (endoscopic, using diathermy or cold punch), with or without cystoscopy and with or without urethroscopy, and including services to which item 36854, 37201, 37202, 37207, 37208, 37303, 37321 or 37324 applies(Anaes.) Fee: $1,002.70 Benefit: 75% = $752.00

Category 3 – THERAPUTIC PROCEDURES
MBS 37206 PROSTATECTOMY (endoscopic, using diathermy or cold punch), with or without cystoscopy and with or without urethroscopy, and including services to which item 36854, 37303, 37321 or 37324 applies, continuation of, within 10 days of the procedure described by item 37201, 37203 or 37207 or which had to be discontinued for medical reasons (Anaes.) Fee: $536.95 Benefit: 75% = $402.75

Open prostatectomy (OP)

Open prostatectomy (OP) is performed in men with large prostates (estimated size greater than 80–100 gram) or in those for whom hip or other medical conditions preclude the physical positioning required for TURP. OP is performed through a lower abdominal incision, and either through the bladder or through the capsule of the prostate. A general or spinal anaesthetic is required. In Australia, OP is carried out much less frequently than TURP, representing a much smaller cost to the MBS. It involves a longer hospital stay and increased risk of bleeding in comparison to TURP. It does however have lower re-treatment rates and no risk of TUR syndrome. A general or spinal anaesthetic is required.

The current MBS item descriptors for OP are:

Category 3 – THERAPUTIC PROCEDURES
MBS 37200 PROSTATECTOMY, open (Anaes.) (Assist.) Fee: $977.80 Benefit: 75% = $733.35

Other treatments

In addition to the core surgical options described, a number of other minimally invasive techniques exist for treating BPH. These include high-intensity focused ultrasound, transurethral laser coagulation of the prostate, transurethral electro-vaporisation of the prostate, transurethral ethanol ablation of the prostate, water-induced thermotherapy, and bipolar resection of the prostate. To date, three minimally invasive procedures have been included on the MBS. These are: visual laser ablation of the prostate, transurethral needle ablation and transurethral microwave therapy. These are described briefly below.

Visual laser ablation of the prostate (VLAP)

The 'Greenlight' laser is considered to be the main laser that is used for visual laser ablation of the prostate. This laser vaporises the prostate by employing rapid localised heating with minimal depth of penetration. It uses a high-powered potassium titanyl phosphate (KTP) laser that is selectively absorbed by tissue with high haemoglobin content (such as prostatic tissue).

Laser vaporisation of the prostate can be performed with a range of anaesthesia, ranging from a local prostate block with intravenous sedation to general anaesthesia. It requires operating room preparation and facilities, and is performed by a urologist with the assistance of an anaesthetist and nursing staff (Kuntz 2006).

In 2010–11, 939 MBS claims for VLAP were made (including MBS items 37207 and 37208). This procedure has been MBS-listed since July 1995. There has been increasing use of this item in recent years as a result of increased uptake of the Greenlight laser.

Transurethral needle ablation (TUNA)

TUNA is used to ablate prostate tissue. It involves the delivery of radiofrequency energy via a modified urethral catheter attached to a generator. Two adjustable needles located at the end of the catheter are inserted into the prostate under endoscopic control. The radio frequency energy passes via the needles through the prostate. This causes a localised heating and results in areas of coagulative necrosis, which either slough via the urethra or are re-adsorbed during tissue repair. The procedure is performed under local or regional anaesthetic and an indwelling catheter is required for up to three days. TUNA can be performed as a day surgery (Medical Services Advisory Committee 2002).

TUNA is restricted to men who are not fit for TURP due to high operative risk. TUNA was assessed by MSAC in 2002 and recommended for interim funding for three years, linked to the acquisition of data (Medical Services Advisory Committee 2002). TUNA was again considered by MSAC in March 2010, and public funding was supported indefinitely. This was based on the clinical support for the intervention, the international evidence and the small likelihood that sufficient Australian evidence could be collected for a full MSAC assessment. TUNA is used very infrequently in Australia. In 2010–11, only four MBS claims were made.

Transurethral microwave thermotherapy (TUMT)

TUMT uses microwave thermotherapy and is similar to TUNA in that it uses heating of the tissue to cause areas of coagulative necrosis. The procedure is typically performed using an antenna mounted within a transurethral catheter, through which cooling fluid circulates. TUMT can be performed in a day-stay setting, using local anaesthesia and oral analgesia along with sedation. Post-operative catheterisation varies from one to two weeks (Medical Services Advisory Committee 2005).Forty-three MBS claims were made in 2010–11.

Transurethral incisional prostatectomy (TUIP)

TUIP is a treatment for relieving urinary outflow obstruction caused by BPH. An incision is made just distal to the ureteral orifice on one or both sides and ends just proximal to the verumontanum. The incisions are made in order to 'open up' the urinary channel, allowing urine to flow more freely. TUIP involves no prostate tissue removal (unlike both TURP and OP) (Jepsen & Bruskewitz 1998). TUIP however is considered to be only suitable for men with estimated smaller prostate sizes (<30g) (Cornford et al 1998).This procedure has been MBS-listed since 1991.

Marketing status of device

At present, 12 holmium:YAG laser devices are TGA-registered and listed on the Australian Register of Therapeutic Goods (ARTG). Three tissue morcellators are also TGA-registered and listed on the ARTG.

Current reimbursement arrangements

HoLEP is not currently reimbursed in the public or private setting. It is available in some private hospitals through self-pay arrangements.

Approach to assessment

Objective

The aim of this assessment is to examine the evidence of safety, effectiveness and cost-effectiveness of HoLEP (with or without tissue morcellation) so as to inform a decision as to whether it should be listed on the MBS as a surgical option in the treatment of benign prostatic hyperplasia.

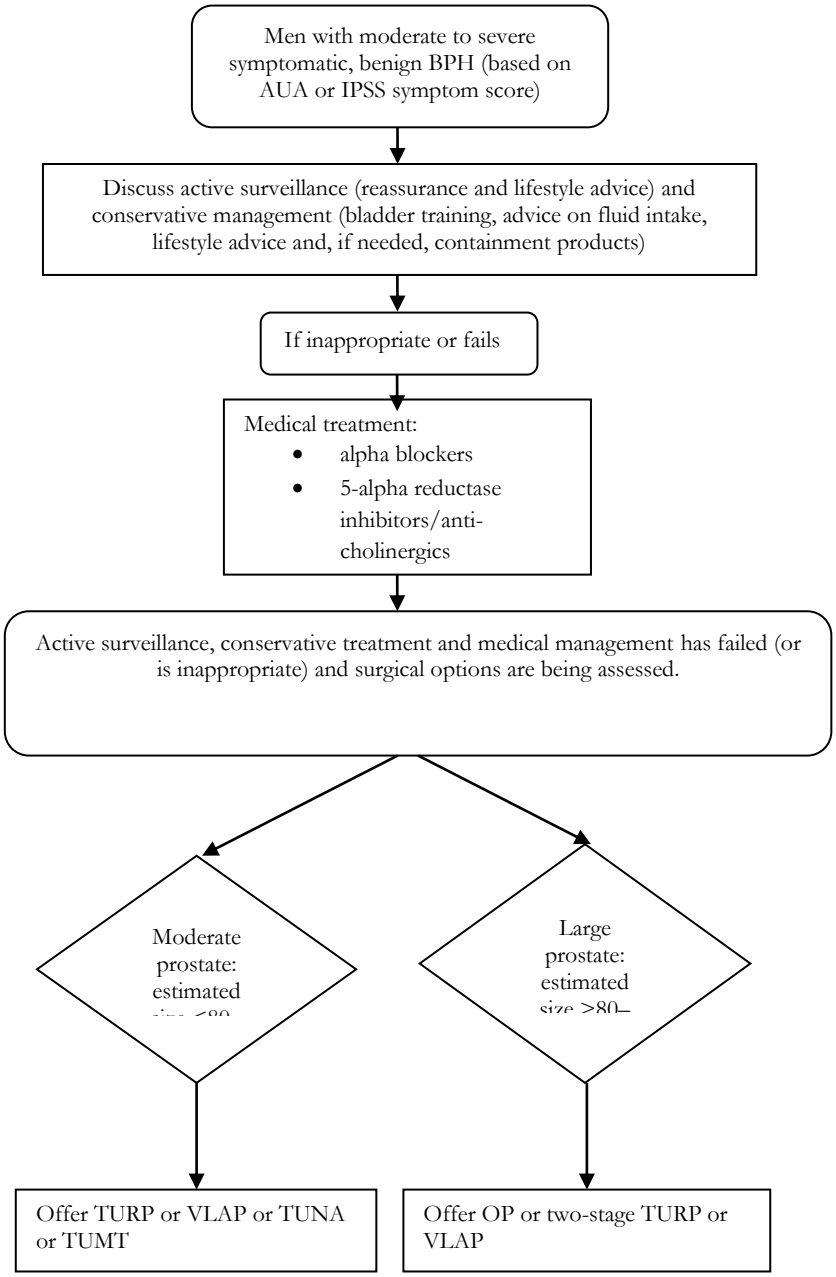
A decision analytic protocol (DAP) was developed prior to the commencement of the assessment, and was approved by the Protocol Advisory Sub-Committee of MSAC (MSAC 2011).The purpose of a DAP is to describe in detail a limited set of decision option(s) associated with the possible public funding of a proposed new medical service. A DAP also captures the current clinical practice and reflects the likely future practice with the proposed new medical service, and describes all potentially impacted healthcare resources. The guiding framework of the DAP has been used throughout this assessment.

Clinical decision pathway

The current clinical management pathway in Australia for men with BPH is depicted in Figure 3. Patients with moderate to severe BPH (based on AUA or IPSS score[1]) are initially managed through active surveillance (with lifestyle advice where appropriate) or through first-line pharmacologic therapy. The patient is referred for second-line surgical intervention where drug therapy has failed or it is inappropriate. Surgical options for men with moderate-size prostates (<80–100 g) include TURP or VLAP or TUNA or TUMT. Surgical options for men with larger prostates (>80–100 g) include OP or two-stage TURP or VLAP.

[1]American Urological Association Symptom Score or the International Prostate Symptom Score. Moderate symptoms are defined as a score between 8 and 19 and severe symptoms are defined as a score between 20 and 35.

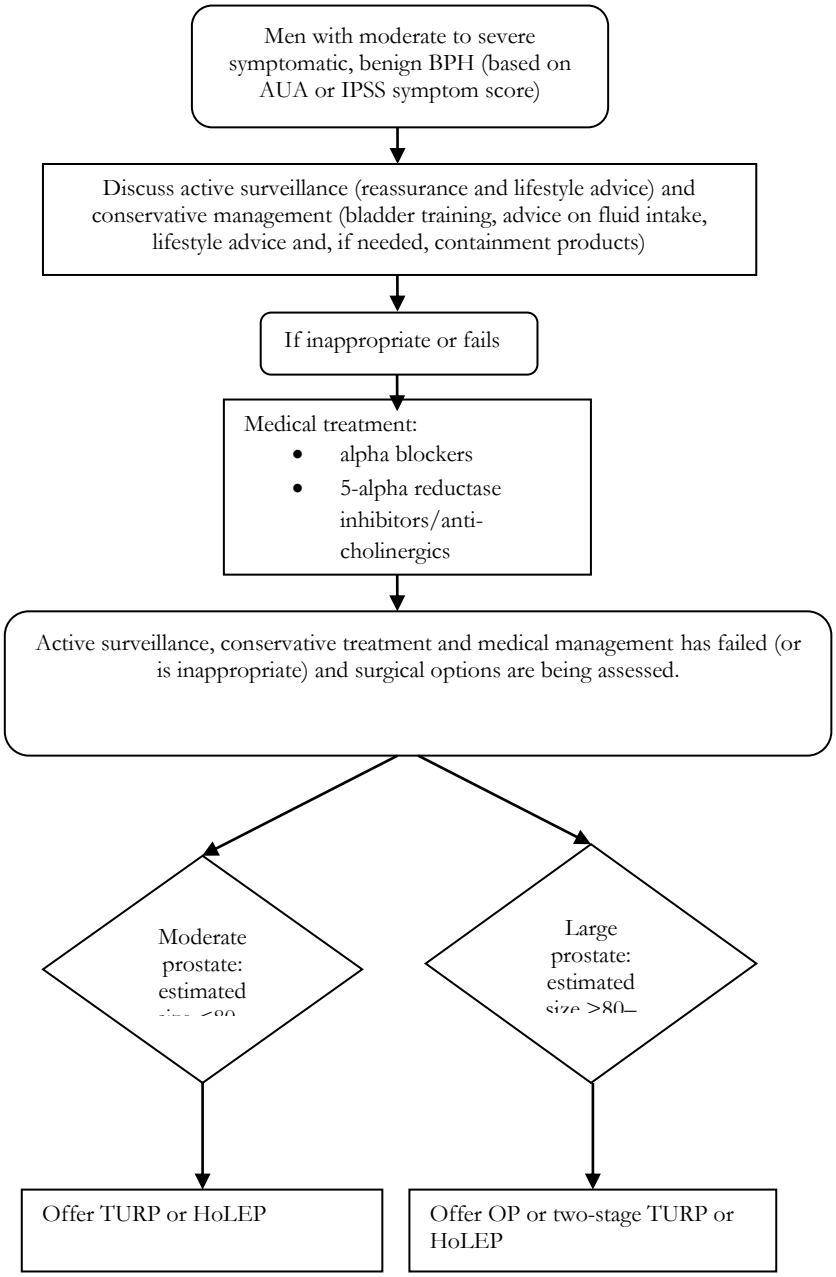
Figure 3: Current clinical management chart for patients with BPH



Comparator

An alternative clinical management pathway depicting the basis for selecting the comparator is shown in Figure 4. This pathway would apply in the event that HoLEP were approved for public funding. It is proposed that HoLEP would represent a surgical alternative to TURP in those with moderate prostate sizes, and an alternative to OP or two-stage TURP in those with larger prostates.

Figure 4: Proposed clinical management chart for patients with BPH



VLAP, TUNA, and TUMT are comparable procedures. Due to their low utilisation rates and small costs to the MBS relative to TURP or OP, however, they are not considered as suitable comparators for this assessment and so are not included in the proposed clinical algorithm. Further, HoLEP would be expected to replace these procedures in centres where it is available. This approach is described in the DAP and was approved by PASC.

Research questions (decision options)

The questions for public funding addressed in this review are:

In men with symptomatic BPH no longer manageable with medications, and with an expected prostate size less than 80–100 g, what is the safety, effectiveness and cost-effectiveness of HoLEP (with or without tissue morcellation) in comparison to TURP?

In men with symptomatic BPH no longer manageable with medications, and with an expected prostate size greater than 80–100 gram, what is the safety, effectiveness and cost-effectiveness of HoLEP (with or without tissue morcellation) in comparison to open prostatectomy?

Review of literature

Prior to conducting the search strategy of the medical literature for original research papers, a search of the websites of international health technology assessment (HTA) agencies was initially conducted so as to identify any existing HTA reports. This identified nine HTA reports that were relevant to this assessment (Appendix E).

The report of Lourenco et al (2008) was updated in the comparison of HoLEP with TURP. This is considered to be a high-quality systematic review, and was published by the UK National Institute for Health Research (NIHR) Health Technology Assessment programme. The report included literature up to 2006 and identified five randomised controlled trials (RCTs) that compared HoLEP with TURP. As a result, the search of the medical literature conducted for this assessment was limited to articles published from 2006. Table 8 lists the electronic databases of published research that were searched for this review.

The Australian and New Zealand Horizon Scanning Network (ANZHSN) review was chosen for updating in the assessment of HoLEP in comparison with OP(2010). This report was not considered to be of high quality (Table 14, page 27) despite being based on a comprehensive search strategy. It was considered however that this report could be relied on to identify any literature published prior to 2006 despite methodological limitations/weaknesses. Of note, this report also compared HoLEP with TURP. Despite being published subsequently to Lourenco, the latter study was chosen in this comparison due to the methodological high quality.

Databases included in both of these searches are shown in Table 8 below. The search terms and search strategy are shown in Appendix C.

Table 8: Electronic databases searched

Database	Period covered
EMBASE (includes EMBASE and MEDLINE)	2006–26 October 2011
PreMedline	2006–26 October 2011
All EBM Reviews (includes: Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts and Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CCTR), NHS Economic Evaluation Database (CLEED), Health Technology Assessment (CLHTA), Cochrane Methodology Register (CLMCR))	2006–26 October 2011

Search strategy

The search strategy was developed using the key elements of the clinical question as described in the DAP. As it was known that RCT evidence was available, a search filter was applied. The search terms and search strategy for the databases above are shown in Appendix C.

Reference lists of included publications were also checked for any additional studies.

Selection criteria

The search strategy identified a total of 204 citations. The citations were evaluated by two independent reviewers who determined whether the studies met the eligibility criteria as listed in Box 1 below. Discrepancies in the results of the screening process were resolved by discussion.

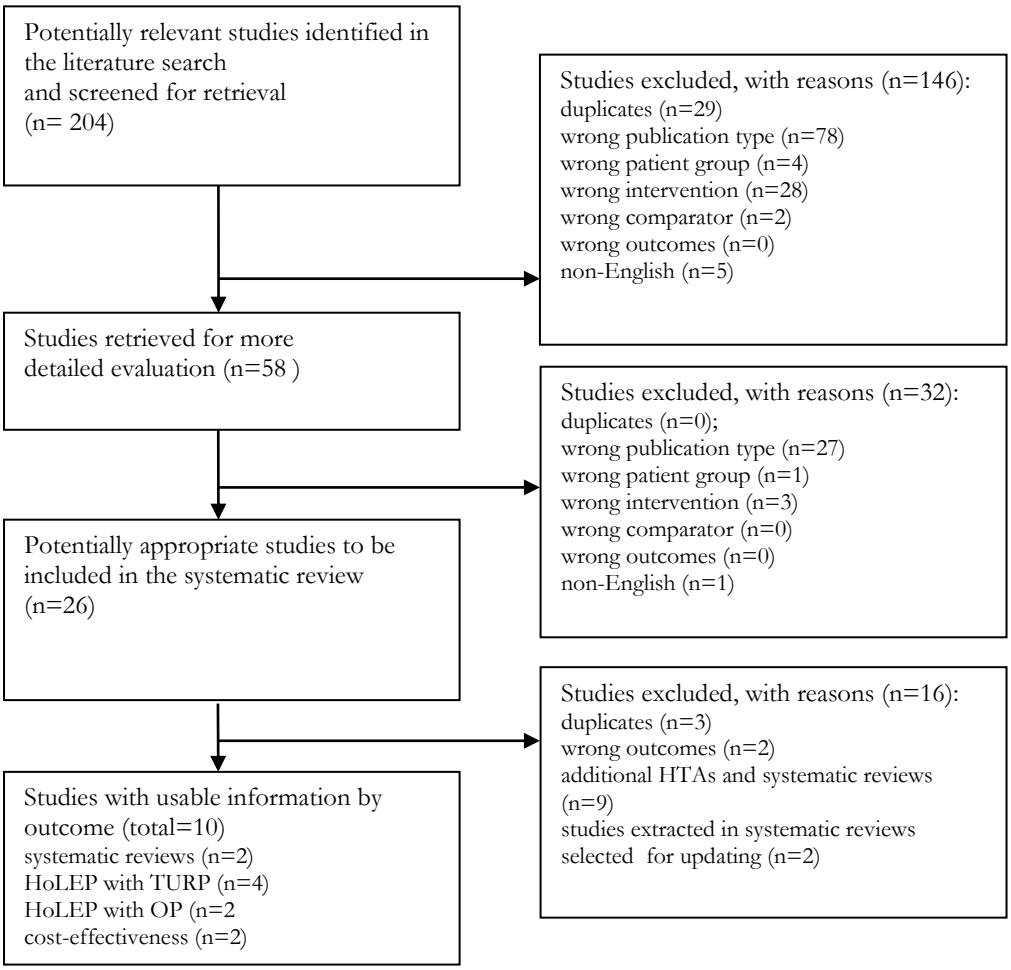
Box 1 Selection criteria for included studies

Selection criteria	Inclusion	Exclusion
Publication type	Systematic reviews, meta-analyses, randomised controlled trials, economic analyses	All other studies
Patients	Patients with symptomatic BPH or lower urinary tract symptoms (LUTS) of the prostate, which were no longer manageable with medications Mixed patient studies with ≥70% BPH or LUTS patients were included Studies with ≥20 patients were included	All others
Intervention	Holmium laser enucleation of the prostate (HoLEP)	Other interventions
Comparator	One (or both) of the following: - open prostatectomy (OP) - transurethral resection of the prostate (TURP)	All other comparators
Outcomes	Studies had to report on at least one of the following outcomes: - safety: immediate complications (bleeding, acute urinary retention, infection, TUR syndrome, mortality) - safety: longer term complications (urethral stricture, erectile dysfunction, urinary incontinence) - effectiveness (symptoms, including peak flow, symptom score, bother score, post-void residual volume, prostate volume, quality of life, treatment failure/re-treatment rate) - cost (length of operation, length of catheterisation, length of hospital stay, training, equipment, staffing)	Studies failing to report on at least one of these were excluded
Language	English	Non-English language studies were excluded

Search results

The quorum flowchart for this search is shown in figure 5 below.

Figure 5: Search results – Quorum flowchart



Adapted from Moher et al (1999)

Data extraction and analysis

Data were extracted by one researcher and checked by a second, using standardised data extraction tables developed prior. Data were extracted only when clearly indicated in tables, text or figures in the study.

Appraisal of the evidence

Appraisal of the evidence was conducted at three stages:

Stage 1: Appraisal of the applicability and quality of individual studies included in the review.

Stage 2: Appraisal of the precision, size and clinical importance of the primary outcomes used to determine the safety and effectiveness of the intervention.

Stage 3: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (2000).

These dimensions (Table 9) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 9: Evidence dimensions

Type of evidence	Definition
Strength of the evidence Level Quality Statistical precision	The study design used, as an indicator of the degree to which bias has been eliminated by design.* The methods used by investigators to minimise bias within a study design. The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

Strength of the evidence

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence.

Level

The 'level of evidence' reflects the effectiveness of a study design to answer a particular research question. Effectiveness is based on the probability that the design of the study has reduced or eliminated the impact of bias on the results.

The NHMRC evidence hierarchy provides a ranking of various study designs ('levels of evidence') by the type of research question being addressed (Table 10).

Table 10 Designations of levels of evidence according to type of research question (including table notes)(NHMRC 2009)

Level	Intervention[1]	Diagnostic accuracy [2]	Prognosis	Aetiology[3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪non-randomised, experimental trial[9] ▪cohort study ▪case-control study ▪interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors among persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪non-randomised, experimental trial ▪cohort study ▪case-control study
III-3	A comparative study without concurrent controls: ▪historical control study ▪two or more single-arm study[10] ▪interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪historical control studies ▪two or more single-arm studies
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Source: NHMRC 2009.

Table notes

1Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b).

2The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

4A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

8All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

10Comparing single arm studies i.e., case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

11Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Quality appraisal/assessment of risk of bias

The quality of a study refers to the extent to which it has been designed and conducted to reduce bias in the estimation of outcomes.

As it was determined that the report by Lourenco et al (2008) was a high-quality systematic review, reappraisal of the studies identified was not undertaken. Studies that were identified in the updated literature search that were follow-up studies to the ones included in that review were also not appraised for quality. Lourenco states that studies were assessed using a tool based on the schema suggested by the NHS Centre for Reviews and Dissemination, Verhagen and colleagues, Downs and Black and the Generic Appraisal tool for Epidemiology.

The studies reported in the ANZHSN however were appraised for quality/risk of bias. This is because assessment of quality is not undertaken as part of a horizon scanning report.

Assessment of risk of bias in the studies referred to above was undertaken using the 'risk of bias' tool developed by the Cochrane Collaboration (Higgins et al 2008). This includes five domains of bias: selection, performance, attrition, detection and reporting, as well as an 'other bias' category to capture other potential threats to validity. Reporting bias however is not included as a domain in this report as trial protocols have not been identified as part of this assessment. Each domain is assigned a judgment of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias. Each judgment should be supported by a statement from the trial such as verbatim quotes. Studies are assessed as at unclear risk of bias when too few details are available to make a judgment of 'high' or 'low' risk.

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000). Studies need to be appropriately designed to ensure that a real difference between groups will be detected in the statistical analysis.

Size of effect

In examining the effects of HoLEP, it was important to assess whether statistically significant differences between the comparators were also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects.

Data analysis

All meta-analyses were carried out using Review Manager Version 5.1 (RevMan) for Windows. Meta-analysed results are presented as mean difference (MD) ± standard deviation (SD) for all continuous outcomes. For dichotomous outcomes, relative risk (RR) is presented with 95% confidence intervals (CI). Analyses were conducted using the random-effects method. Results were considered to be of statistical significance if $p<0.05$. Heterogeneity was measured using a chi-squared test for heterogeneity and the I^2 statistic. To investigate heterogeneity the I^2 statistic, given by the formula $[(Q - df)/Q] \times 100\%$, where Q is the chi-squared statistic and df is its degrees of freedom, is used (Higgins et al 2008). This measure describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). The I^2 statistic quantifies the inconsistency across trials and enables an assessment of the impact of the heterogeneity on the meta-analysis. A value greater than 50% may be considered to indicate substantial heterogeneity (Higgins et al 2008).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development(NHMRC 2009).

Five components are considered essential by the NHMRC when judging the body of evidence:

- The evidence base – which includes the number of studies sorted by their methodological quality and relevance to patients.

- The consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction, that is homogenous or heterogeneous findings.

- The potential clinical impact –appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test.

- The generalisability of the evidence to the target population.

- The applicability of the evidence –integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 11)(NHMRC 2009).

Table 11: Body of evidence assessment matrix

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or an SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population	Population/s studied in the body of evidence are similar to the target population	Population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Adapted from (NHMRC 2009).

Expert advice: Health Expert Standing Panel (HESP)

HESP has been established as a panel of the Medical Services Advisory Committee (MSAC) and is a pool of experts collated from various medical fields who are nominated by their associated professional body or by applicants.

HESP members are engaged to provide practical, professional advice to evaluators which directly relates to each application and the service being proposed for the MBS. HESP members are not members of either MSAC or its subcommittees ESC and PASC. Their role is limited to providing input and guidance to the assessment groups to ensure that the pathway is clinically relevant and takes into account consumer interests. HESP member's advice is to inform the deliberations MSAC presents to the Minister.

Results of assessment

Systematic reviews and health technology assessments

The list of electronic databases and websites searched for systematic reviews and HTAs is provided in Appendix C. Nine systematic reviews and HTAs that compared HoLEP with TURP and/or OP met the inclusion criteria. Four of these systematic reviews and HTAs compared HoLEP with TURP and five compared HoLEP with TURP and OP. As outlined previously, the systematic review of Lourenco et al (2008) was chosen for updating in this assessment for the comparison of HoLEP with TURP. The Australian and New Zealand Horizon Scanning Network (ANZHSN) 2010 review of the current state of development of laser prostatectomy was chosen for updating in the comparison of HoLEP with OP.

The other systematic reviews that compared HoLEP with TURP either included the same studies as the Lourenco et al report or were not considered of high methodological quality. Similarly the reviews assessing HoLEP and OP were either of lower quality or reported the results for OP in combination with TURP. All of these systematic reviews and HTAs are listed in Appendix E. They are not however further considered as part of this report.

Approach to assessing HoLEP in comparison with TURP

Lourenco et al (2008): This is a high-quality systematic review, developed as part of the UK National Institute for Health Research (NIHR) Health Technology Assessment programme. Its objective was to determine the clinical and cost-effectiveness (in the UK) of alternative surgical treatments to TURP. It identified a number of RCTs providing a direct comparison of HoLEP with TURP in men with BPH. The characteristics and quality assessment of this systematic review is summarised in

Table 12 below.

Table 12: Characteristics and quality appraisal of Lourenco et al 2008

Author Year Country	Studies included	Methods	Quality assessment
Lourenco et al (2008) UK	Gupta et al (2006) Kuntz et al (2004) Montorsi et al (2004) Tan et al (2003)/Wilson et al (2006) Westenberg et al (2004)	Databases searched: 13 databases, incl. MEDLINE, EMBASE, MEDLINE In-Process, BIOSIS, ISI Science Citation Index, ISI Proceedings, Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, HTA Database, National Research Register, Clinical Trials, Current Controlled Trials. Also conference proceedings of: European Assoc. of Urology, the American Urological Assoc., British Assoc. of Urological Surgeons Time period of search: 1966–2006 Comparators: HoLEP vs TURP Outcomes: safety, effectiveness, cost-effectiveness	**Quality: High** Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: Yes Heterogeneity between studies assessed: Yes Summary of main results clear and appropriate: Yes

The updated literature search carried out as part of this assessment identified four further studies that met the inclusion criteria. These therefore added to the evidence provided by Lourenco et al. Of these, two were longer term follow-ups of some of the studies included in the systematic review and two were new.

The characteristics of each of the additional RCTs updating the Lourenco et al systematic review listed above are summarised in Table 13.

While the general approach to this assessment was to update the results of the Lourenco et al report, further detail was needed for the economic model in respect to incontinence, stricture and re-operation rates. As such for these outcomes, the original studies included in the Lourenco report were reviewed.

Table 13: Characteristics of studies not included in the Systematic Review

Follow up studies to those included in the Lourenco et al., 2008 systematic review				
Study	**N**	**Study design**	**Population**	**Description**
Ahyai et al (2007) (follow-up to Kuntz et al (2004))	HoLEP: 100 TURP: 100	RCT	Patients with AUA score ≥12, Q max ≤12 ml/s, PVR volume ≥50 ml, Schafer grade ≥2 and total prostate volume <100 cc.	Kuntz et al (2004) presents data up to 12 months post-surgery. This follow-up presents information at 2 years and 3 years. Three year numbers to follow-up n=75 (HoLEP) and n=69 (TURP). This study compared HoLEP with mushroom technique (rather than tissue morcellation) to TURP. Outcomes: peak flow, AUA symptom scores and PVR
Gilling et al (2011) (follow-up to Tan et al (2003))	HoLEP: 31 TURP:30	RCT	Patients with prostate volume between 40–200 ml, Qmax ≤15 ml/s, AUA score ≥8, PVR<400ml and Schafer grade ≥ 2.	Tan et al (2003) presents data up to 12 months post-surgery. This follow-up presents information at 2 years and 4 years. 4 year numbers to follow-up n=14 (HoLEP) and n=17 (TURP). Outcomes: peak flow, AUA symptom score, quality of life and treatment failure/re-treatment rate
New studies identified in the literature searches				
Study	**N**	**Study design**	**Population**	**Description**
Eltabey et al(2010)	HoLEP: 40 TURP: 40	RCT	Patients with BOO caused by BHP, with related voiding symptoms, prostate size between 30–100 g , who had not responded to pharmacologic therapy, with AUA symptom score ≥12 and Qmax ≤15ml/s.	Outcomes reported at 1, 6 and 12 months post-surgery. HoLEP (with tissue morcellation) compared to TURP. Safety outcomes: blood transfusion urethral stricture incontinence. Effectiveness outcomes: peak flow AUA symptom scores PVR prostate volume Cost-related outcomes: length of operation length of catheterisation length of hospital stay
Mavuduru et al (2009)	HoLEP: 15 TURP: 15	RCT	Patients eligible for surgery for symptomatic BPH	Outcomes at 3 months and 9 months post-surgery. HoLEP (morcellation was only used in one patient) compared to TURP. Safety outcomes: blood transfusion

				capsular perforations urethral stricture incontinence Effectiveness outcomes: IPSS symptom scores PVR prostate volume) Cost-related outcomes: length of operation length of catheterisation

BOO = Bladder outlet obstruction; PVR=post-void residual volume; AUA score=American Urological Association score; Qmax=peak urinary flow rate.

Quality assessment

The two additional new studies identified in the updated literature search relevant to the comparison between HoLEP and TURP had an unclear risk of bias. While sequence generation was undertaken by a computer generated table, allocation concealment was not described. No details were given regarding blinding of patients, personnel or outcomes assessors, although this is not unusual in surgery trials (McCulloch et al 2002). It is unlikely however that lack of blinding will have a significant impact on the reported results as the majority of the primary measures of effectiveness are functional outcomes. Follow-up of patients (attribution bias) was generally not well reported.

Approach to assessing HoLEP in comparison to OP

The systematic review undertaken by the ANZHSN was undertaken to examine the current state of development of laser prostatectomy. The report constitutes the most extensive comparison of HoLEP and OP that met the inclusion criteria, and could therefore be used for updating of the HoLEP and OP outcomes. The report also compared HoLEP and TURP. Although published more recently, the studies identified in the review had either been used by Lourenco et al or had been independently identified in this assessment. This systematic review was therefore not chosen over Lourenco et al in the analysis of HoLEP with TURP. The characteristics and quality assessment of this ANZHSN review is summarised in Table 14 below.

In addition to the studies included in this review, three other non-randomised comparative studies were also reported. These however did not meet the inclusion criteria.

No additional studies were identified in the literature search. Consequently, the assessment of comparative safety and effectiveness of HoLEP and OP is based on the two RCTs referred to above.

Quality assessment

The two RCTs included in the assessment of HoLEP in comparison with OP were also assessed in terms of risk of bias. Both these studies had an unclear risk of bias due to the lack of details described in terms of randomisation and blinding. Sequence generation was reported for both but no further details were given in respect to allocation

concealment. Blinding of patients, personnel or outcomes assessors was not described. Reasons for loss to follow-up were not given in the paper by Naspro et al (2006). They were however listed in Kuntz et al (2008).

Table 14: Characteristics and appraisal of ANZHSN report

Author Year Country	Studies included	Methods	Quality assessment
ANZHSN (2010) Australia	Naspro et al (2006) Kuntz et al (2008)	Databases searched: AustHealth, Australian Medical Index, CINAHL, Cochrane Library, Current Contents, Embase, Pre-Medline, Medline, PsychINFO, RACS electronic library. 11 HTA websites were also searched. Time period of search: to 20 March 2010 Comparators: HoLEP vs TURP and OP Outcomes: safety, effectiveness, cost-effectiveness	Quality: Low Explicit review questions: No Explicit & appropriate eligibility criteria: No Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: No. Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: Yes

Is it safe? HoLEP compared with TURP

Pooling of information with respect to rates of blood transfusion, urethral stricture and incontinence was possible based on the data extracted from the studies identified in the Lourenco et al review and those identified in the updated literature search. A summary of this information is provided in Table 15 below. Lourenco et al also analysed data in relation to acute urinary retention and urinary tract infection. The further studies identified in this review did not report on these outcomes. Accordingly, a summary of these results from the Lourenco et al analysis are included in the Table 15.

Table 15: Safety outcomes: HoLEP in comparison with TURP

Outcome	Studies (n)	Patients HoLEP /TURP (n)	HoLEP (total events)	TURP (total events)	Estimate of effect	Range (95% CI)*	I^2 (%)	p-value
Blood transfusion rate	7	348/342	1	13	RR 0.27	0.09–0.85	0	0.02
Urethral stricture	7	322/309	14	23	RR 0.65	0.33-1.27	0	0.21
Incontinence	6	306/296	7	8	RR 0.84	0.31–2.28	0	0.97
Acute urinary retention*	5	293/287	15	21	RR 0.71	0.38–1.32	8	0.28
Urinary tract infection*	2	91/89	5	5	RR 0.98	0.31–3.09	37	0.97

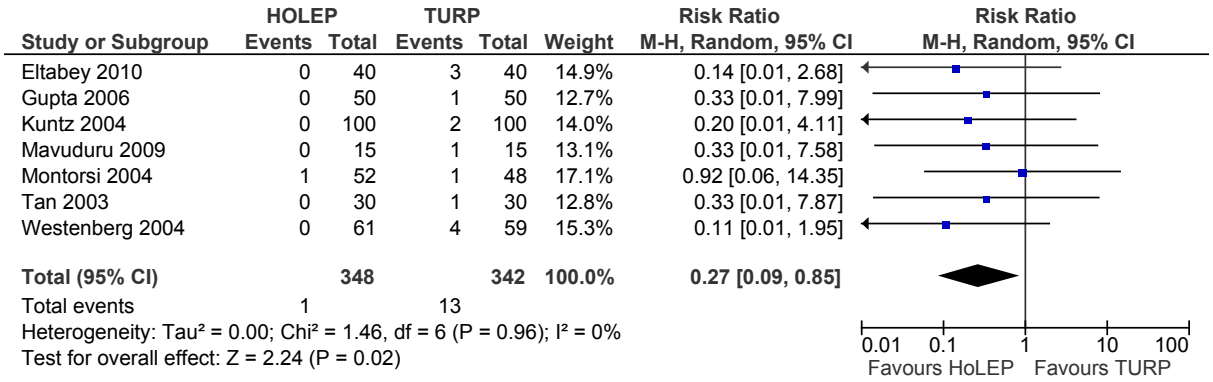
RR= relative risk;* Results are from Lourenco et al (2008)as no additional data were reported in the more recent studies.

Forest plots for bleeding, urethral stricture and incontinence are set out below.

Blood transfusion rates

The data in Figure 6 below show statistically significant differences in the rate of blood transfusions between the two interventions, favouring HoLEP.

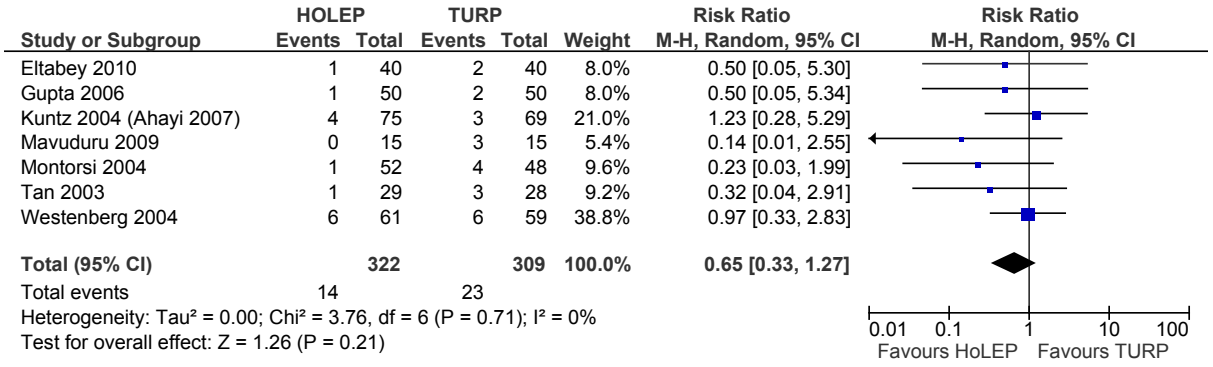
Figure 6: Blood transfusion rates: HOLEP compared with TURP



Urethral stricture

The data in Figure 7 below show there was no statistically significant difference between the treatments with respect to stricture. It should be noted that the below data also includes bladder neck stenosis as for some trials it was difficult to distinguish between the complications based on the information reported. The rates of urethral stricture in some of the individual studies were also reported at different timelines or simply recorded at last follow-up. In the Lourenco meta-analysis, stricture is reported as "after surgery". Eltabey et al (2010) record stricture at 12 months while Mavuduru et al (2009) report rates at three weeks and at three and nine months. The paper by Ahayi et al (2007) also includes additional patients at a follow-up of 36 months to that presented in Kuntz 2004.

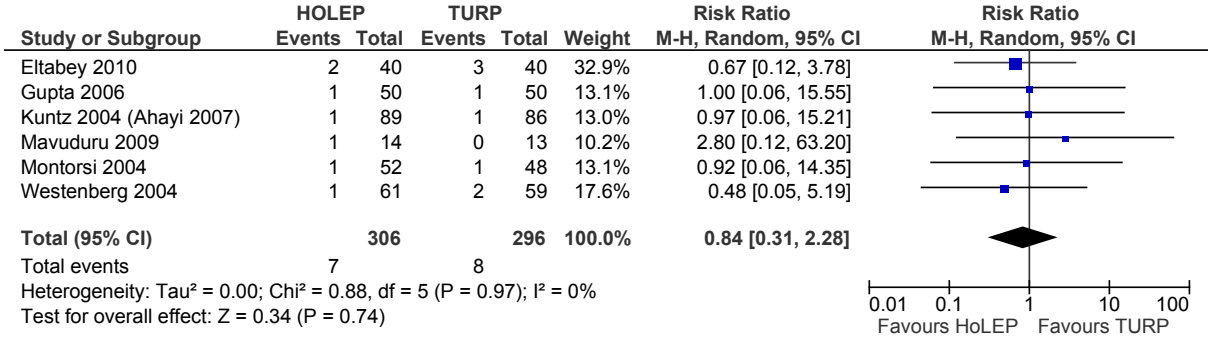
Figure 7: Urethral stricture: HOLEP compared with TURP



Incontinence rates

The data in Figure 8 below show there was no statistically significant difference between the treatments with respect to incontinence. Lourenco notes that studies typically failed to identify what type of urinary incontinence patients had and in the Lourenco analysis transitory incontinence had been pooled together with urge and de novo stress incontinence. The below figure excludes cases of transitory incontinence and urge incontinence (where it was described). As such it is likely that these rates are more indicative of long-term incontinence in patients following either HoLEP or TURP. Rates were also reported at different time points with most studies reporting at 6 months or less, with the longest follow-up reported by Westernberg (2004) at 48 months.

Figure 8: Incontinence rates: HOLEP compared with TURP



It was not possible to pool results for a number of safety outcomes that were included in the DAP due to the paucity of data in a number of cases. These include:

TUR syndrome: Lourenco et al 2008 report that the rates of TUR syndrome were lower for HoLEP (n=0, 0.0%) than for TURP (n=1, 2.08%) based on one study. The results were not statistically significant (p=0.47).

Mortality: Lourenco et al 2008 report that mortality rates were slightly lower in the HoLEP group(n=1, 1.10%) than for TURP (n=2, 2.25%) based on two studies. The difference was not statistically significant (p=0.61). It is unclear from the report when these deaths occurredand if there were related to the procedure or recorded during follow-up and therefore unrelated to treatment.

Erectile dysfunction: Lourenco et al 2008 report that erectile dysfunction rates were higher for the HoLEP group (n=2, 9.09%) than for TURP (n=2, 7.69%) based on a single study. The results were not statistically significant (p=0.86).

Dysuria: Dysuria was included in the DAP as a potential adverse event associated with either intervention. In the study by Mavuduru et al (2009) transient dysuria was reported following catheter removal in one patient in the HoLEP group (6.7%) compared to three patients treated with TURP (20%).

Capsular perforation: Lourenco et al 2008 report that capsular perforation rates were higher for the HoLEP group (n=1, 2.0%) than for TURP (n=0, 0%) based on a single study. In the small study by Mavuduru et al (2009) capsular perforation occurred in one patient in the HoLEP group. Statistically significant differences were not reported. This outcome was not listed in the DAP.

Two areas of uncertainty can arise in the interpretation of safety outcomes that are extracted only from RCTs. Less frequently observed complications that may be reported in larger cohort studies may not be identified. Longer term, or less frequently observed, complications also may not be reported in shorter term trials. In the latter case however follow-up data subsequently published to the original RCTs provide more robust estimates of complications. This was in line with the approach adopted by Lourenco et al (2008).

The time point of recording of urinary stricture and urinary incontinence was not well defined. These adverse events were pooled together in this assessment despite this limitation. The results reported should be interpreted within this context.

Summary of safety of HoLEP versus TURP

In comparison with TURP, HoLEP appears to be as safe as TURP across a range of outcomes assessed. HoLEP offers statistically significant advantages over TURP in relation to blood transfusion rates postprocedure. The evidence from the systematic review and two additional RCTs suggests that differences in the rates of other adverse events are not statistically significant. Some caution should be exercised in the interpretation of this information given the wide confidence intervals that exist around some of the outcomes.

Is it effective? HoLEP compared with TURP

Pooling of data with respect to peak flow, IPSS/AUA symptom score, post-void residual volume (PVR) and treatment failure/re-treatment rates was possible based on the data extracted from the studies identified in the Lourenco et al report and those additional studies identified. In all pooled outcomes this updated evidence comprised one additional study not identified in Lourenco et al (Eltabey et al (2010)) or longer term follow-up data to that already cited in Lourenco et al (Ahayi et al 2007, an update of Kuntz 2004). Data have only been presented from six months onwards. Earlier data (one, three months) or data outside common time points (nine months) are presented in Appendix D.

A summary of pooled effectiveness outcomes is provided in Table 16 below.

Table 16 Effectiveness outcomes: HoLEP compared with TURP

Outcome	Studies (n)	Patients HoLEP /TURP (n)	HoLEP (mean)	TURP (mean)	Estimate of effect (MD)	Range (95% CI)*	I2 (%)	p-value
Qmax @ 6 months(ml/s)	6	323/315	24.2	23.3	0.99	-0.81–2.80	62	0.28
Qmax @ 12 months(ml/s)	6	317/310	25	23.4	1.39	0.64–2.15	9	0.002
Qmax @ 24 months (ml/s)	3	147/142	24.7	23.1	1.14	-2.17–4.46	41	0.5
IPSS/AUA @ 6 months (score)	6	323/315	4.0	4.4	-0.66	-1.34–-0.03	71	0.06
IPSS/AUA @ 12 months (score)	6	295/296	3.6	4.4	-0.96	-1.73–-0.18	80	0.02
IPSS/AUA @ 24 months (score)	2	125/116	2.6	3.8	-1.49	-3.29–0.32	63	0.11
PVR volume @ 6 months (mls)	3	160/158	14.7	28.7	-11.9	-14.74–-9.17	0	<0.001
PVR volume @ 12 months (mls)	2	129/126	5.3	25.4	-19.4	-25.55–-13.16	0	< 0.001
Treatment failure/re-treatment**	2	91/89	1**	5**	0.27	0.04-1.60	0	0.15
Quality of life @ 6 months*	3	139/136	1.2	1.2	0.25	0.05–0.44	77.3	0.01
Quality of life @ 12 months*	3	138/134	1.3	1.3	0.06	-0.26–0.38	86.2	0.73
Quality of life @ 24 months*	2	67/67	1.1	1.1	-0.01	-0.40–0.38	0	0.96

PVR= post-void residual volume; MD=weighted mean difference; RR=relative risk;* results are from Lourenco et al (2008).as no additional data were reported in the more recent studies; **total number of events, rather than mean.

The study by Mavuduru et al (2009) identified in the updated literature search and not included in Lourenco, reports on effectiveness outcomes at 3 and 9 months. It is therefore not included in the pooled data at 6, 12 and 24 months below. The results are however outlined in Appendix D.

Forest plots are set out below.

Peak flow (Qmax)

These data shown in figures 9, 10 and 11 indicate a statistically significant difference between the interventions at 12 months, favouring HoLEP. Differences at 6 and 24 months however do not show significant differences. The latter results should be interpreted with caution however due to the higher degree of heterogeneity across the studies at these time points. Three studies reported on longer-term follow-up in respect to peak flow. These were Ahyai et al 2007 reporting at 36 months, Westenberg et al 2004 at 48 months and Gilling et al 2011 reporting at 92 months (Appendix D). All three studies reported that at final follow-up patients treated with HoLEP had an increase in peak flow compared to those in the TURP, although these differences were not significant.

Figure 9: Qmax at 6 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI	Year
Tan 2003	26.4	9.2	26	20.8	12.4	29	7.6%	5.60 [-0.13, 11.33]	2003
Montorsi 2004	23.1	8.6	52	26.5	15.5	48	9.4%	-3.40 [-8.37, 1.57]	2004
Westenberg 2004	23.9	8.7	61	22.4	9	59	16.2%	1.50 [-1.67, 4.67]	2004
Kuntz 2004	25.1	6.9	94	25.1	9.4	89	20.6%	0.00 [-2.40, 2.40]	2004
Gupta 2006	23.1	1.2	50	20.7	1.32	50	31.7%	2.40 [1.91, 2.89]	2006
Eltabey 2010	23.5	9.2	40	24.3	6.8	40	14.4%	-0.80 [-4.35, 2.75]	2010
Total (95% CI)			**323**			**315**	**100.0%**	**0.99 [-0.81, 2.80]**	

Heterogeneity: Tau² = 2.62; Chi² = 13.02, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 1.08 (P = 0.28)

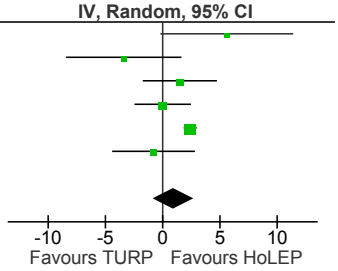


Figure 10: Qmax at 12 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Eltabey 2010	24.9	11.7	40	25.5	7.4	40	0.0%	-0.60 [-4.89, 3.69]
Tan 2003	21.8	10.5	25	18.4	14.5	27	1.8%	3.40 [-3.45, 10.25]
Westenberg 2004	25.2	11.9	61	20.4	8.5	59	5.8%	4.80 [1.11, 8.49]
Montorsi 2004	25.1	7.2	52	24.7	10	48	6.7%	0.40 [-3.04, 3.84]
Kuntz 2004	27.9	9.9	89	27.7	12.2	86	7.2%	0.20 [-3.10, 3.50]
Gupta 2006	25.1	1.06	50	23.7	1.58	50	78.5%	1.40 [0.87, 1.93]
Total (95% CI)			**277**			**270**	**100.0%**	**1.48 [0.56, 2.40]**

Heterogeneity: Tau² = 0.21; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 3.16 (P = 0.002)

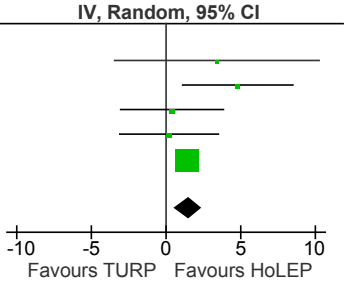
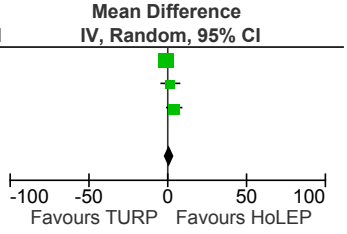


Figure 11: Qmax at 24 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Ahayi 2007	28	9	80	29.1	10.9	75	46.2%	-1.10 [-4.26, 2.06]
Tan 2003	21	9.38	22	19.3	11.22	26	23.0%	1.70 [-4.13, 7.53]
Westenberg 2004	25	11	45	20.9	11.1	41	30.8%	4.10 [-0.58, 8.78]
Total (95% CI)			**147**			**142**	**100.0%**	**1.14 [-2.17, 4.46]**

Heterogeneity: Tau² = 3.58; Chi² = 3.39, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 0.68 (P = 0.50)



Symptoms scores (IPSS/AUA)

The data in Figures 12, 13 and 14 below indicate that at there were statistically significant differences between the interventions that favoured HoLEP at 6 and 12 months. There was however a high degree of heterogeneity across all of the studies. Longer term follow-up of patients was available at 36 months (Ahyai et al 2007), 48 months (Westenberg et al 2004) and at 92 months (Gilling et al 2011). At all three time points patients treated with HoLEP had lower symptom scores in comparison to patients in the TURP group, although these differences were not significant.

Figure 12: Symptom score at 6 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Eltabey 2010	2.6	1.3	40	3.8	3.1	40	17.1%	-1.20 [-2.24, -0.16]
Gupta 2006	5.2	0.31	50	6.1	0.42	50	27.8%	-0.90 [-1.04, -0.76]
Kuntz 2004	2.2	1.6	94	3.7	3.7	89	19.9%	-1.50 [-2.33, -0.67]
Montorsi 2004	3.9	2.9	52	2.9	2.6	48	16.6%	1.00 [-0.08, 2.08]
Tan 2003	6	5.09	26	4.8	3.77	29	6.4%	1.20 [-1.19, 3.59]
Westenberg 2004	3.8	3.8	61	5	4.5	59	12.1%	-1.20 [-2.69, 0.29]
Total (95% CI)			**323**			**315**	**100.0%**	**-0.66 [-1.34, 0.03]**

Heterogeneity: Tau² = 0.44; Chi² = 17.32, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 1.87 (P = 0.06)

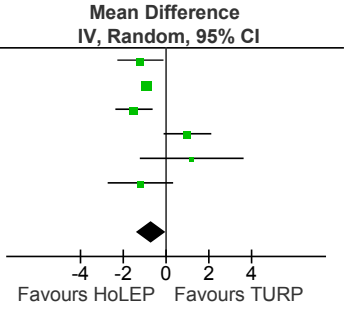


Figure 13: Symptom score at 12 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Eltabey 2010	2.2	1.4	40	3.7	1.6	40	22.0%	-1.50 [-2.16, -0.84]
Gupta 2006	5.2	0.17	50	5.6	0.32	50	26.1%	-0.40 [-0.50, -0.30]
Kuntz 2004	1.7	1.8	89	3.9	3.9	86	19.2%	-2.20 [-3.11, -1.29]
Montorsi 2004	3.9	3.6	48	4.1	2.3	52	16.1%	-0.20 [-1.39, 0.99]
Tan 2003	4.3	3.5	25	5	4.68	27	8.2%	-0.70 [-2.94, 1.54]
Westenberg 2004	4.2	6	43	4.3	4.1	41	8.4%	-0.10 [-2.29, 2.09]
Total (95% CI)			**295**			**296**	**100.0%**	**-0.96 [-1.73, -0.18]**

Heterogeneity: Tau² = 0.59; Chi² = 25.37, df = 5 (P = 0.0001); I² = 80%
Test for overall effect: Z = 2.43 (P = 0.02)

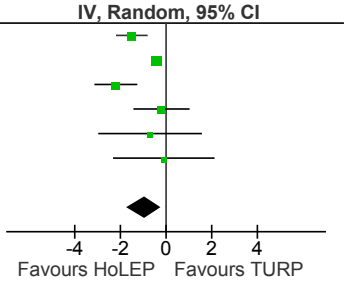
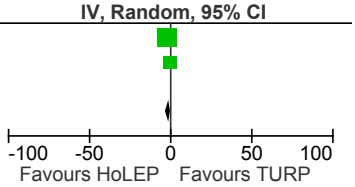


Figure 14: Symptom score at 24 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Ahayi 2007	1.7	1.7	80	3.9	3.7	75	62.5%	-2.20 [-3.12, -1.28]
Westenberg 2004	3.4	4.9	45	3.7	4.9	41	37.5%	-0.30 [-2.37, 1.77]
Total (95% CI)			**125**			**116**	**100.0%**	**-1.49 [-3.29, 0.32]**

Heterogeneity: Tau² = 1.14; Chi² = 2.70, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 1.62 (P = 0.11)



Post-void residual volume

The data in Figures 15 and 16 show statistically significant differences between the treatments at 6 and 12 months, favouring HoLEP. Ahyai et al (2007) provide follow-up data at 24 months and 36 months. At final follow-up patients treated with HoLEP had a significantly lower PVR compared to patients treated with TURP (8.4 mls ± 26.0 versus 20.2 ± 33.0 p<0.012).

Figure 15: PVR at 6 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Eltabey 2010	5.7	12.6	40	17.6	18.3	40	27.9%	-11.90 [-18.79, -5.01]
Kuntz 2004	4.8	12.5	94	16.7	16.9	89	70.7%	-11.90 [-16.23, -7.57]
Tan 2003	33.7	28	26	51.8	78	29	1.4%	-18.10 [-48.46, 12.26]
Total (95% CI)			**160**			**158**	**100.0%**	**-11.99 [-15.63, -8.35]**

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 6.46 (P < 0.00001)

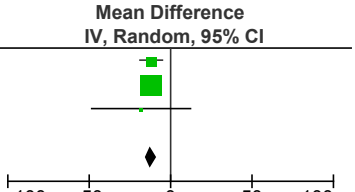
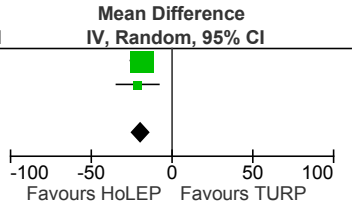


Figure 16: PVR at 12 months: HoLEP compared with TURP

Study or Subgroup	HoLEP Mean	HoLEP SD	HoLEP Total	TURP Mean	TURP SD	TURP Total	Weight	Mean Difference IV, Random, 95% CI
Eltabey 2010	5.3	15.2	40	24.1	16.8	40	77.8%	-18.80 [-25.82, -11.78]
Kuntz 2004	5.3	15.3	89	26.6	60.4	86	22.2%	-21.30 [-34.46, -8.14]
Total (95% CI)			**129**			**126**	**100.0%**	**-19.35 [-25.55, -13.16]**

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 6.12 (P < 0.00001)



Treatment failure/re-treatment rates

The general approach in this assessment was to update the results of the Lourenco et al report. This report however did not specifically extract data on treatment failure and re-treatment rates as outlined in the DAP. Lourenco instead reported on re-operation rates which included revision of the original procedure as well as surgical intervention for other complications such as stricture. It was decided that a review of data in the studies

included in the Lourenco et al report for these outcomes would be undertaken to ascertain treatment failure/re-treatment rates. Re-operation rates are also reported for completeness (see Appendix G).

Only two trials reported that patients had surgical revision or a second procedure for the symptoms of BPH. Both trials were from centres in Australasia. Tan et al (2003) states that one patient in the TURP group remained obstructed and underwent HoLEP after 11 months while no treatment failures were reported in the original HoLEP group. In the trial by Westenberg et al (2004) it is reported that one patient in the HoLEP group and 4 patients in the TURP group underwent revision (RR 0.27, 95% CI 0.04–1.60, p=0.15). Ahyai et al (2007) state that while one patient experienced BPH recurrence following HoLEP the patient refused re-operation because of absence of discomfort. In the follow-up study of Gilling et al (2011), which updated Tan et al (2003), one additional failure is reported in the TURP group. The two new studies identified in the updated literature search do not discuss treatment failures.

Lourenco et al 2008 included the results of four trials when assessing re-operation rates. As mentioned above, this included both surgical revision and re-operation for complications. No statistically significant differences were observed (RR 0.68, 95% CI 0.32–1.44, p=0.31).

Quality of life

Data from quality of life studies were assessed in the Lourenco et al report based on data (IPSS QoL 0-6 questionnaire) from three studies. At three months, no statistical significance between HoLEP and TURP was reported. At 12 months, evidence from the studies showed marked heterogeneity present in the meta-analysis, and the direction of effect was not consistent. At two and four years, there appeared to be no differences between the interventions. More recently, Gilling et al (2011) have published longer term follow-up data on QoL. It was reported that at 92 months patients in the HoLEP group had slightly higher scores than those in the TURP group, although statistical significance was not reported (see Appendix D).

It was not possible to pool results for a number of other effectiveness outcomes due to the paucity of data in a number of cases. These include:

Prostate volume: It is difficult to draw conclusions from the available evidence for differences in effectiveness between HoLEP and TURP with regard to prostate volume for any of the time intervals reported. 'Prostate volume' was rarely reported in the identified literature. It was understood differently across those studies where it was reported. Within studies, statistically significant differences were not reported (Tan et al 2003), were not significant (Eltabey et al 2010) or were significant (Mavuduru et al 2009).

Bother scores: Although included in the DAP as an effectiveness outcome to be assessed, none of the studies included in this review reported on bother scores.

Secondary effectiveness outcomes

In this review, HoLEP and TURP were also compared with respect to operative outcomes. These include length of operation, length of catheterisation, length of hospital stay, training cost, and equipment cost and staffing cost (

Table 16).

Table 16: Secondary effectiveness outcomes: HoLEP compared with TURP

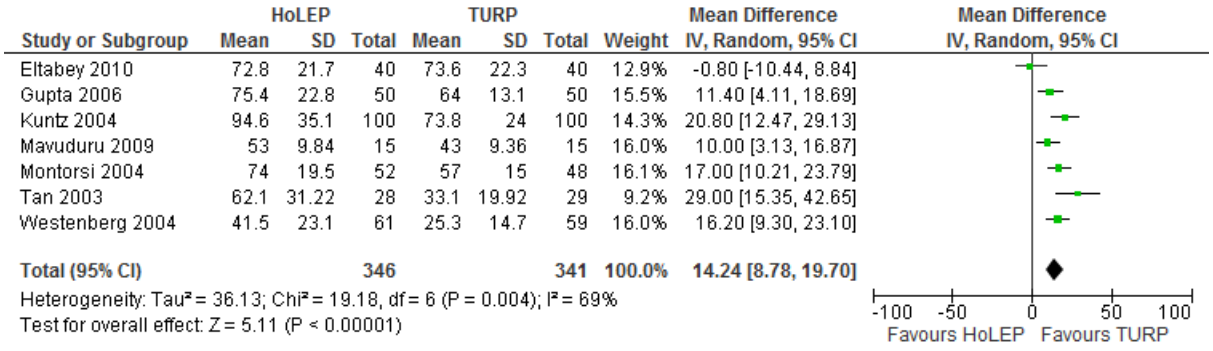
Outcome	Studies (n)	Patients HoLEP /TURP (n)	HoLEP (mean)	TURP (mean)	Estimate of effect (MD)	Range (95% CI)*	I^2 (%)	p-value
Duration of operation (min)	6	331/336	70	54.6	15.8	8.70–21.46	72	p<0.000 01
Duration of catheterisation (hours)	6	285/282	31.1	53.4	22.39	28.18–16.60	80	p<0.000 01
Duration of hospital stay (days)	5	281/276	1.9	3.0	1.08	1.26–0.89	28	p<0.000 01

Forest plots are set out below.

Duration of operation

As shown in Figure 17, six studies report that the duration of operation was longer for HoLEP than for TURP, with statistically significant differences in all cases. One study (Eltabey et al 2010) reports slightly shorter operation time for HoLEP than for TURP; however, the results are not statistically significant and there is significant heterogeneity across the studies. Pooling the results indicates that mean operative time was significantly longer in the HoLEP group than in the TURP group. Surgeon experience was often not noted in the studies and so it difficult to ascertain whether these results would reflect current operative times.

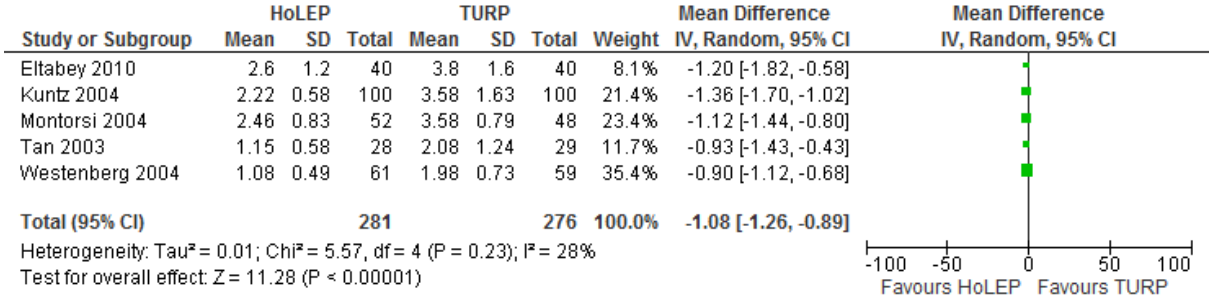
Figure 17: Duration of operation: HoLEP compared with TURP



Duration of hospital stay

As shown in Figure 18, all five studies consistently report shorter hospital stay for HoLEP than for TURP with statistically significant differences.

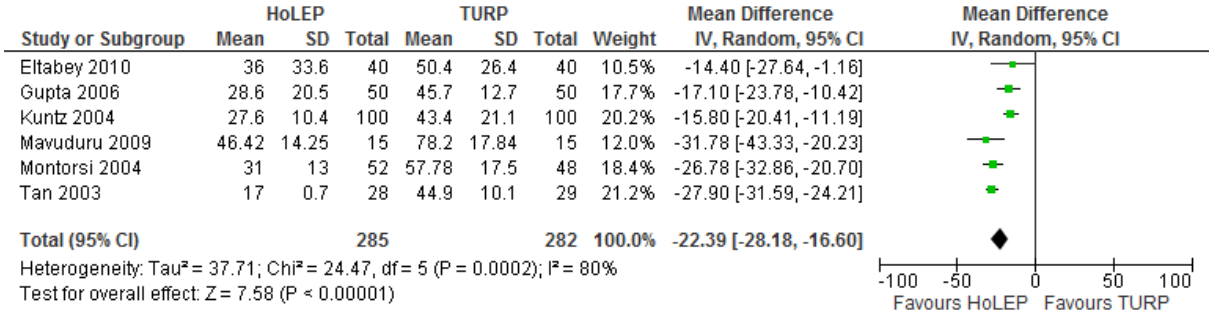
Figure 18: Duration of hospital stay: HOLEP compared with TURP



Length of catheterisation

As shown in Figure 19, all six studies consistently report shorter catheterisation time for HoLEP than for TURP, with statistically significant differences but a high degree of heterogeneity. The estimate of effect between the groups however may be overestimated by differences in how the procedures were performed.

Figure 19: Duration of catheterisation: HoLEP compared with TURP



Other outcomes

None of the studies included in this evaluation considered the other outcomes listed in the DAP (training, equipment and staffing costs).

Summary of effectiveness of HoLEP versus TURP

HoLEP appears to be as effective, or more effective, than TURP across a range of effectiveness outcomes. These include peak flow (Qmax), symptom scores and PVRs. Quality of life differences and differences in respect of treatment failure/re-treatment rates between the interventions were not significant.

A HoLEP procedure takes longer to complete than a TURP procedure, but is associated with a statistically significant shorter hospital stay. Catheterisation times are also shorter.

Is it safe? HoLEP compared with OP

Primary safety outcomes

Short-term complications assessed in this report include blood transfusion rates, acute urinary retention, infection and mortality. Longer term complications include urethral stricture, erectile dysfunction and urinary incontinence.

Table 17 outlines the primary safety outcomes reported in the studies.

Table 17: Safety outcomes: HoLEP compared with OP

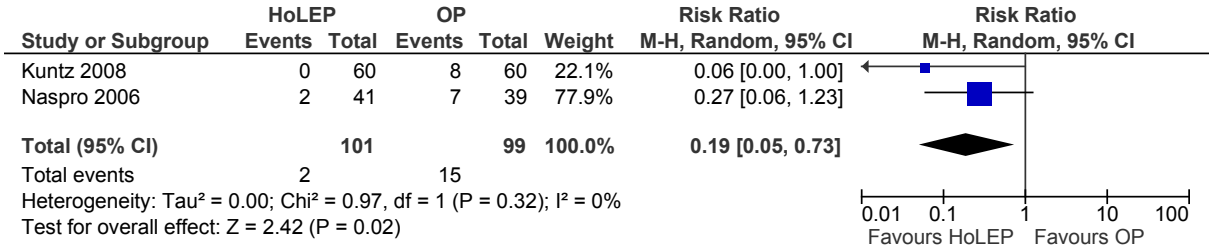
Outcome	Studies (n)	Patients HoLEP /OP (n)	HoLEP (total events)	OP (total events)	Estimate of effect (RR)	Range (95% CI)*	I^2 (%)	p-value
Blood transfusion rates	2	101/99	2	15	0.19	0.05–0.73	0	p=0.02
Urethral stricture	2	101/88	5	4	1.07	0.30–3.87	0	p=0.91
Incontinence	2	97/99	7	9	0.79	0.31–2.04	0	p=0.63

Sufficient data were available to pool the results for blood transfusion rates, urethral stricture and incontinence.

Bleeding (blood transfusion)

In a meta-analysis of the two studies, patients allocated to HoLEP were less likely to have a blood transfusion that than those allocated to OP as outlined in Figure 20.

Figure 20: Blood transfusion rates: HoLEP compared with OP



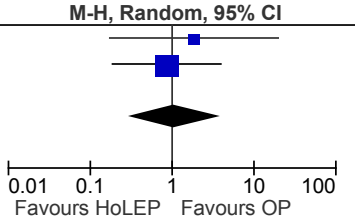
Urethral stricture

Urethral stricture was reported in both studies at various time points and the data below includes all reported cases regardless of when the event occurred. The majority (n=8) occurred past 12 months (see Appendix D). Rates were similar between HoLEP and OP patients and no statistically significant differences were found between the two groups in terms of incidence of strictures.

Figure 21: Urethral stricture: HoLEP compared with OP

Study or Subgroup	HoLEP Events	HoLEP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI
Kuntz 2008	2	53	1	49	29.3%	1.85 [0.17, 19.76]
Naspro 2006	3	35	3	30	70.7%	0.86 [0.19, 3.94]
Total (95% CI)		**88**		**79**	**100.0%**	**1.07 [0.30, 3.87]**
Total events	5		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)



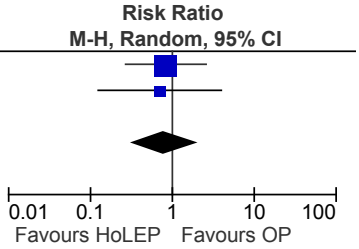
Incontinence

Combining the data from the study showed no significant differences between the two groups in respect to incontinence. The data in Figure 22 below do not include rates of transitory incontinence which was reported in both studies (Appendix D).

Figure 22: Incontinence: HoLEP compared with OP

Study or Subgroup	HoLEP Events	HoLEP Total	OP Events	OP Total	Weight	Risk Ratio M-H, Random, 95% CI
Kuntz 2008	5	60	6	60	70.1%	0.83 [0.27, 2.58]
Naspro 2006	2	37	3	39	29.9%	0.70 [0.12, 3.97]
Total (95% CI)		**97**		**99**	**100.0%**	**0.79 [0.31, 2.04]**
Total events	7		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)



Pooling was not feasible for the remaining outcomes due to the lack of data. These include:

Erectile dysfunction: Naspro et al (2006) report that there was no significant reduction in IIEF scores[2]from baseline in the follow-up period (24 months) in either HoLEP or TURP patients. Kuntz et al (2008) do not report erectile dysfunction in the complications section of the study. It was noted in the discussion section however that there were no significant differences in sexual function between the two groups at 3,6,12 or 18 months.

Acute urinary retention: Naspro et al 2006 reported that in the HoLEP group, five patients (12.1%) experience urinary retention in comparison to two patients (5.1%) in the OP group.

Dysuria: Naspro et al 2006 reported that at three months 28 patients (68.2%) in the HoLEP group experienced dysuria compared to 16 patients in the OP group (41%). At 12 months this rate had decreased to 10.8% and 8.5% in the HoLEP (4/41) and OP (3/39) group respectively.

Infection and procedure-related mortality were not described in either of the studies.

Other adverse events reported in the studies included three cases of bladder mucosal injury in patients undergoing HoLEP(Naspro et al 2006).

[2]International Index of Erectile Function.

Summary of safety of HoLEP versus OP

The evidence on safety is based on two RCTs of 200 people (101 HoLEP and 99 OP).

In a meta-analysis of the two studies, patients allocated to HoLEP were less likely to have a blood transfusion that than those allocated to TURP. Other complications, such as incontinence and stricture, were comparable between the groups.

Is it effective? HoLEP compared with OP

Outcomes assessed in the comparison of HoLEP with OP included peak flow, symptom score, bother score, PVR, prostate volume and quality of life scores. Rates of treatment failure/re-treatment were also assessed. Pooling of data for three outcomes (Qmax, IPSS and treatment failure) was possible and these are listed below (Table 18). Statistically significant differences associated with either intervention were not demonstrated at any time period in any of the outcomes.

Table 18: Effectiveness outcomes: HoLEP compared with OP

Outcome	Studies (n)	Patients HoLEP /OP (n)	HoLEP (mean)	OP (mean)	Estimate of effect (MD)	Range (95% CI)*	I2 (%)	p-value
Qmax @ 12 months(ml/s)	2	93/84	24.9	26.3	1.53	3.51–0.45	0	p=0.13
Qmax @ 24 months (ml/s)	2	88/79	23	23.8	0.78	3.10–1.54	0	p=0.51
IPSS/AUA @ 12 months (score)	2	93/84	5.4	5.4	0.01	0.79–0.81	0	p=0.99
IPSS/AUA @ 24 months (score)	2	88/79	5.1	5.3	0.11	0.98–0.76	0	p=0.80
Treatment failure/re-operation	2	97/95	5*	6*	0.82	0.26–2.59	0	P=0.73

* Total number of events rather than mean; MD=mean difference

Forest plots are set out below.

Peak flow (Qmax)

Pooling of data at 12 and 24 months is shown in figures 23 and 24. Longer term follow-up is reported by Kuntz et al (2008). At 36 months, 48 months and 60 months mean peak flow is comparable between the group. At final follow-up at five years mean peak flow is 24.3 ± 10.10 in the HoLEP group and 24.4 ± 7.4 in the OP group p=0.97.

Figure 23: Qmax at 12 months: HoLEP compared with OP

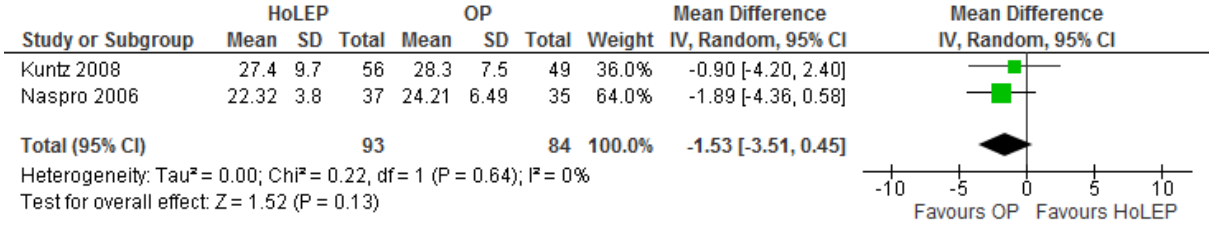
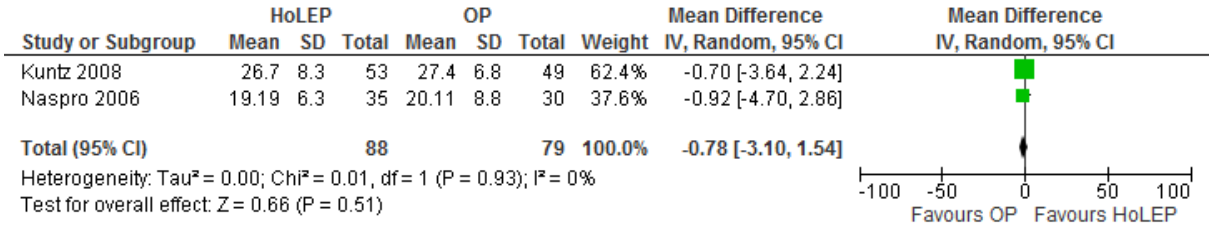


Figure 24: Q max at 24 months: HoLEP compared with OP



Symptom scores

Symptom scores at 12 months and 24 months are shown in figures 25 and 26. Comparable changes in symptom scores were obtained within each of the interventions, with no statistically significant differences between the groups. Kuntz et al (2008) report that this change is maintained at up to five years (3.00 ± 3.2 in the HoLEP group compared to 3.00 ± 1.7 in the OP group p=0.98).

Figure 25: Symptom scores at 12 months: HoLEP compared with OP

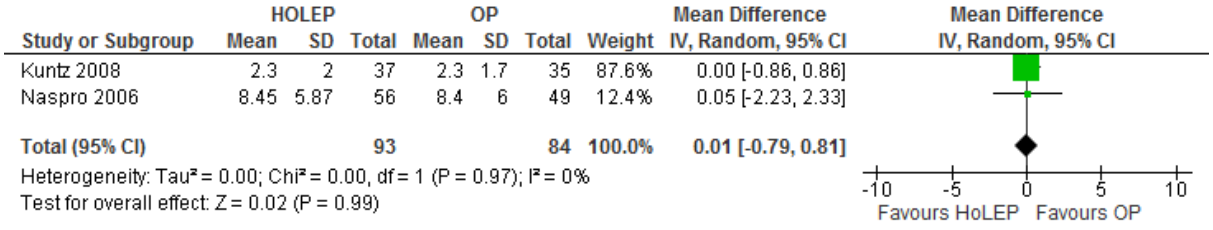
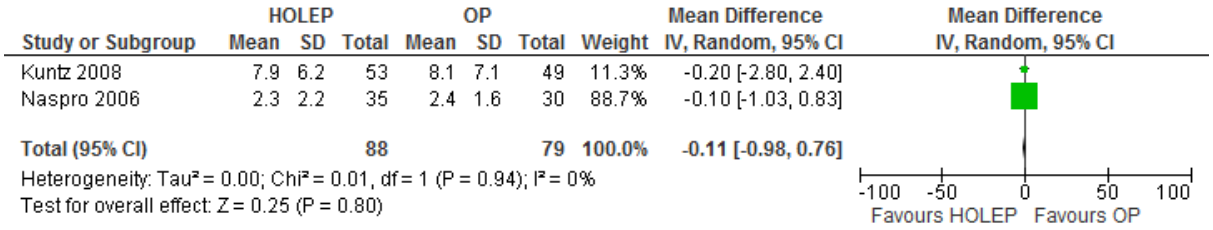


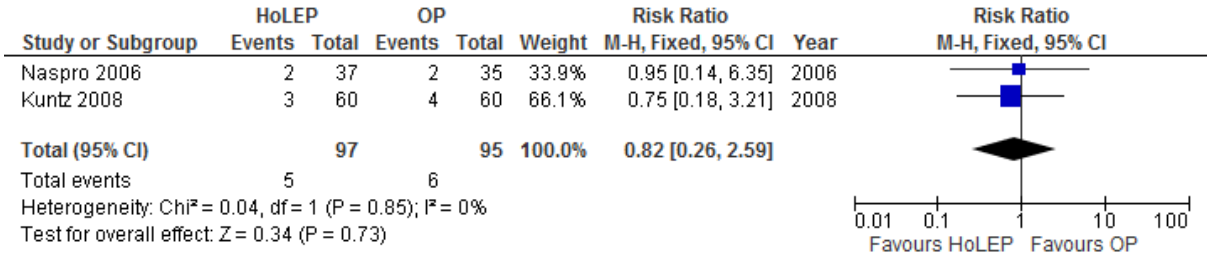
Figure 26: Symptom scores at 24 months: HoLEP compared with OP



Treatment failure/re-operation rates

Treatment failure/re-operation rates are shown in figure 27. Naspro et al (2006) report that the overall reintervention rate at 12 months was 5.4% for HoLEP and 5.7% for OP. No other details are provided and it would seem the reintervention is due to other complications such as bleeding and stricture rather than a revision of the original surgery. However this is an assumption and unclear from the report. In the study by Kuntz et al (2008), three patients in the HoLEP group underwent re-operation, including one for bladder neck contracture and two for urethral stricture. In the OP group, there were three bladder neck contractures and one urethral stricture.

Figure 27: Re-operation rates: HoLEP compared with OP



Data were not pooled in respect of a number of other outcomes:

Post-void residual volume (PVR): Only Kuntz et al (2008) reported on PVR. Non-statistically significant differences between the interventions were not reported at baseline, 3 months, 6 months, 12 months, 2 years, 3 years, 4 years or 5 years. These data are shown in Appendix D.

Prostate volume: Prostate volume was reported in terms of the amount of tissue resected. Naspro et al (2006) state that peri-operative specimen weight was 59g in the HoLEP group compared to 86g in the OP group (p=0.0046). Kuntz et al (2008) report no significant differences in terms of resected tissue (94g versus 96g) between the two groups.

Bother scores: Although included in the DAP as a primary effectiveness outcome for either of these interventions, none of the studies included here reported on this.

Quality of life: Naspro et al (2006) reported on quality of life at baseline, 12 and 24 months (Appendix D). No statistically significant differences between the interventions were recorded.

Secondary effectiveness outcomes

HoLEP and OP were also compared with respect to operative outcomes. Outcomes of interest listed in the DAP included length of operation, length of catheterisation, length of hospital stay, training cost, equipment cost and staffing cost. Both studies reported on length of operation, catheterisation and hospital stay. Due to the clinical heterogeneity of these studies in terms of the intervention, results were not pooled. They are described below and summarised in 19. None of the studies included here reported on training, equipment or staffing costs.

Naspro et al (2006) report that catheterisation time (1.5 versus 4.1 days) and hospital stay (2.7 versus 5.4 days) was shorter for HoLEP than for OP patients. Operative time for HoLEP was however longer. Similarly, Kuntz et al (2008) report a longer operative time for HoLEP. They note however that this was because the majority of patients had been operated on according to an earlier mushroom technique. When the use of the mechanical tissue morcellator was introduced, the operative time significantly decreased. Length of catheterisation (1.3 versus 8.1 days) and length of hospital stay (2.9 versus 10.4 days) were also shorter for HoLEP in comparison with OP.

These data are summarised in

Table 19.

Table 19: Secondary effectiveness outcomes: HoLEP compared with OP

Study	Operative outcomes	HoLEP	OP
Naspro et al (2006)	Length of operation	72.09min	58.31min
	Length of catheterisation(days)	1.5	4.1
	Length of hospital stay (days)	2.7	5.43
Kuntz et al (2008); Kuntz&Lehrich (2002)	Length of operation	136 min	91 min
	Length of catheterisation(days)	1.25	8.1
	Length of hospital stay (days)	2.9	10.4

Summary of effectiveness of HoLEP versus OP

Based on the evidence from these two RCTs, HoLEP appears to be as effective as OP across a range of effectiveness outcomes. These include Qmax, symptom scores and PVRs. No evidence of superiority for HoLEP (or OP) was demonstrated from either of the studies.

It was not possible to adequately address, from the data available, the differences between the interventions with respect to quality of life or treatment failure/re-treatment rates.

A HoLEP procedure may take longer to complete than an OP procedure, but may be associated with a shorter hospital stay and shorter catheterisation times. These data should however be interpreted with caution.

Other relevant considerations

Expert opinion

Expert clinicians form the Health Expert Standing Panel provided commentary and advice during the development of this report on a range of issues including

Overall opinion

Experts were strongly in favour of a positive listing of the procedure. HoLEP was described as one of the few surgical procedures for which there is RCT evidence comparing it directly with the gold standards. Long-term RCT data shows that it is at least as effective as TURP, but may be safer and in the long-term and may be associated with a lower rate of re-treatment. The latter was because more tissue can be removed in large prostates compared with TURP, and this has been borne out in the urodynamic data in several of the RCTs which show a greater decrease in obstruction with HoLEP. Procedures for BPH other than HoLEP, including increased use of laser technologies, were considered to be more likely to be used as alternatives to TURP or OP in the future.

The inclusion of "(≥ 100W)" in the proposed item descriptor – "*Endoscopic enucleation of the prostate using high powered (>= 100W) laser and an end-firing, non-contact fibre with or without tissue morcellation*" was considered to be potentially too restrictive. Given that some of the RCTs used high powered lasers that were 80W, and that there are some 50W protocols, the experts considered that the descriptor should say simply "high powered".

Financial considerations

It is difficult to estimate a growth rate, although the introduction of an MBS item number would lead to increase uptake in this technology. There is a learning curve associated with the procedure so this uptake may not be rapid initially. It is something which will probably gradually increase over time. The capital outlay of the equipment is also something that needs to be considered in the uptake of the procedure and also the hospital reimbursement banding for the consumables. If these are made to work in favour of a business model to purchase a high power Holmium laser, then hospitals would be more likely to make this investment. Advantages to hospitals included a reduced length of stay for the procedure, reduced complications and less professional time spent on managing these.

What are the economic considerations?

Economic evaluation

Economic evaluation is important in order to understand both the costs and consequences of introducing a new medical intervention. The introduction of a procedure may be costly, and it is important to ensure that where public funds are limited, those tests which represent the best value for money are identified (Drummond et al 2005). In an economic evaluation, alternative options are compared in terms of their costs and consequences. The most widely used type of economic evaluation is the cost-effectiveness analysis (CEA). In a CEA, consequences are measured in natural or physical units. A cost-utility analysis (CUA) is a specific form of CEA in which the effect of healthcare technologies on life expectancy and health-related quality of life (HRQoL) are combined. The most common outcome measure for a CUA is the quality-adjusted life year (QALY). A CUA is considered the gold standard for economic evaluations because it allows the direct comparison of the relative health benefits of healthcare technologies across different disease areas and populations and therefore facilitates resource allocation decisions (Drummond et al 2005; Gold et al 1999).

To the extent that data allow, a decision-analytic model can be used to synthesise data on costs and consequences obtained from various sources, such as the literature, primary data collected and expert opinion, to estimate the cost-effectiveness or cost per QALY of the new intervention compared to conventional approaches (Briggs et al 2006). In the context of economic evaluation, a decision-analytic model uses mathematical relationships to define a series of possible consequences that would follow from a set of alternative options being evaluated. A key purpose of decision-analytic modelling is to allow for the variability and uncertainty associated with all decisions. Nevertheless, the quality of the model is highly dependent on the quality of information used to populate it.

Literature review

The literature search described in the 'Approach to assessment' section of this report identified two papers that included a formal economic evaluation relevant to this assessment (Lourenco et al 2008;Salonia et al 2006). An overview of these is provided below and in Appendix G. An additional literature search was conducted to identify any further economic evaluations relevant to the assessment of HoLEP compared with TURP or OP. This search strategy combined the MeSH terms used in the search of clinical evidence with search filters developed by the Centre for Reviews and Dissemination to specifically identify publications of economic evaluations. A description of the supplementary search strategy is given in Appendix C.

This supplementary search identified two papers that reported on economic evaluations relevant to the assessment (Stovsky et al 2006;Fraundorfer at al 2001). An overview of these is provided below and in Appendix G.

Economic evaluations comparing HoLEP with TURP

Lourenco et al 2008 (Armstrong et al (2009): The Lourenco et al systematic review referred to in earlier sections of this report also included a wide-ranging economic evaluation of a range of interventions that explored the cost-effectiveness of multiple treatment strategies for BPH. Strategies included in the economic evaluation could be used in various combinations, where patients experiencing treatment failure were eligible to either receive re-treatment using the same method or to receive treatment with another, more invasive, procedure. The economic evaluation was performed through the development of a Markov model. Health states and transition probabilities derived from the meta-analysis of clinical evidence informed the movement of a cohort of 25,000 patients through the model. The time horizon the model was 10 years, with individual cycle lengths of three months.

Results presented were the costs and consequences (QALYs) accrued across the cohort over the time horizon of the model. Only costs incurred from the perspective of the English National Health Service were considered.

For the specific comparison of HoLEP versus TURP, the results indicated that HoLEP was both less costly and more effective than TURP alone (HoLEP is dominant). Across the cohort population of 25,000 patients used in the model, HoLEP treatment was associated with cost savings of £35,082,760 with a corresponding gain of 1,434 QALYs.

A series of results for alternative treatment strategies was also presented. These results do not impact on this assessment as they related to alternative (i.e. non HoLEP, TURP or OP) interventions and have not been summarised here.

Stovsky et al (2006): This American study assessed seven treatment options for BPH including photoselective vaporisation of the prostate (PVP), microwave thermotherapy (TUMT), transurethral needle ablation (TUNA), interstitial laser coagulation (ILC) and transurethral resection (TURP). Unlike the Lourenco et al evaluation, this study did not allow patients to receive more than one treatment option. When initial treatment failed the patient would receive re-treatment with the original technique.

The economic evaluation was performed through the development of a Markov model in which health states and transition probabilities informed the movement of a cohort of 10,000 patients through the model. The time horizon of the model was two years, with individual cycle lengths of one month.

Results presented were the costs accrued across the entire cohort over the duration of the model, as well as the change in clinical outcomes of symptom scores, Qmax and QoL from the pre-treatment baseline. Only costs incurred from the perspective of a third-party payer (US Medicare) were considered.

PVP resulted in the largest benefit in all clinical outcome measures, followed by TURP. The remaining five interventions would be ranked differently according to the clinical outcome measure selected. The numbers of adverse events were not reported as these were used simply to obtain an estimate of the costs. The expected cost (2005 $US) per patient over two years was$3,589 for PVP, $4,754 for ILC, $4,927 for TUNA, $6,179 for TURP and $5,461–$5,699 for TUMT.A synthesis of cost and outcomes facilitating the calculation of the ICER was not presented.

Fraundorfer et al 2001: This study compared HoLRP – holmium laser resection of the prostate. The primary difference between HoLEP and this procedure is the means by which the excised prostatic tissue is removed. This study outlines that HoLEP is associated with a shorter duration of operation and has largely replaced HoLRP as a surgical technique for the treatment of BPH. While this study does not consider HoLEP in comparison to TURP, the high degree of similarity between HoLRP and HoLEP suggests the findings of this study would be broadly applicable to the cost-effectiveness of HoLEP.

This economic evaluation was conducted using clinical and economic data collected from a single-centre clinical trial. One-hundred and twenty patients with BPH and urodynamically proven obstruction were randomised to undergo either TURP (n=59) or HoLRP (n=61). Clinical and economic data were recorded prospectively out to one year postoperatively. The time horizon of the economic evaluation was that of the clinical trial (one year).

Results presented were the total immediate procedural costs associated with HoLRP and TURP, as well as the costs of unplanned clinical visits and inpatient admissions throughout the one-year duration of the trial. The main outcomes assessed were those relating to the immediate treatment with either HoLRP or TURP including resection time (minutes), catheterisation time (hours), nursing contact time (minutes), hospital stay (hours) and blood transfusion (n). Clinical effectiveness measures presented included Qmax (ml/s), symptom score (AUA) and Schafer-grade outcomes at 6 and 12 months. Unscheduled clinic visits, readmissions and complications were also assessed. Only costs incurred from the perspective of the treating hospital were considered in the economic evaluation.

Economic evaluations comparing HoLEP with OP

Only one study was identified that assessed economic aspects of HoLEP treatment as an alternative to OP.

Salonia et al 2006: The aim of this study was to compare the cost of HoLEP with OP in the treatment of BPH in men with a large (70–220g) prostate. The economic data used in this analysis were collected through the conduct of a single-centre clinical trial. In this trial 63 consecutive patients with BPH were randomised to undergo either OP (n=29) or HoLEP (n=34). It is assumed in this study that the time horizon included is only the overall length of stay for the procedure as postoperative clinical and economic data are not presented.

Results presented were the total immediate procedural costs associated with HoLEP and OP. Clinical effectiveness measures for either treatment approach were not presented.

The cost analysis in this study showed a mean cost of €2,868.90 ($US3,556.30) for OP and €2,356.50 ($US2,919.40) for HoLEP, a difference of €512.40 ($US636.90) in favour of HoLEP. A synthesis of cost and outcomes facilitating the calculation of the ICER was not presented.

Discussion of reviewed literature

There is relatively little economic literature relating to HoLEP, and the majority of these papers assess the cost-effectiveness of HoLEP in comparison with TURP. Only Lourenco et al (2008) however specifically reported on both the cost and effectiveness of HoLEP in comparison with TURP. In this evaluation, HoLEP was less costly and more effective than TURP. It is important to note however that this economic evaluation assessed the comparative cost-effectiveness of a range of treatment interventions and clinical management approaches and that a direct assessment of HoLEP against TURP was not the primary focus of this evaluation.

All other studies comparing HoLEP with TURP presented the comparative costs for PVP (not always HoLEP specifically), or for HoLRP and did not include an accompanying synthesis of costs with clinical effectiveness. As such they are not placed to inform the question of the cost-effectiveness of HoLEP compared to TURP. All of the identified economic evaluations indicated that HoLEP (or HoLRP) was a less costly procedure than TURP. Differences in costs were driven primarily by reduced resource use associated with adverse events from the treatment procedure, as well as reduced average length of hospital stay times associated with HoLEP treatment.

The costs presented across the economic evaluations described above were presented from a range of different payer perspectives. As a result of the differences in payer perspective it is difficult to gauge how consistent the results of the published economic evaluations are. Further, the range of payer perspectives used in previous studies impacts on how reliably the costs presented in previous economic evaluations will reflect those incurred in the Australian context and from the perspective of the Federal Government as its role as the primary funder of healthcare in Australia.

The potential issues on the transferability of the results presented in previous economic evaluations to the Australian context leads to the situation whereby the conduct of a cost-effectiveness of HoLEP compared with TURP was undertaken as part of this assessment. This economic evaluation also used data from the updated meta-analysis. The methodological approach to the evaluation followed the parameters outlined in the DAP.

Overall there is a paucity of economic literature evaluating HoLEP treatment compared with OP. Only one publication was identified in the systematic literature review which presented a costing analysis covering the perioperative period only, reporting lower costs associated with HoLEP over OP. As no literature was identified that reported a synthesis of costs and effectiveness for HoLEP compared to OP, the conduct of an economic evaluation assessing the cost-effectiveness of HoLEP compared with OP in the Australian context was undertaken as part of this assessment.

Description of the economic evaluation undertaken

Where applicable, the framework for the economic evaluation conducted in this assessment was aligned with the requirements of the DAP and included:

Study question: There are two decision options (i.e. questions for public funding) listed in the DAP. These are:

- In men with symptomatic BPH no longer manageable with medications, and with an expected prostate size less than 80–100g, what is the cost-effectiveness of HoLEP compared with TURP?

- In men with symptomatic BPH no longer manageable with medications, and with an expected prostate size greater than 80–100g, what is cost-effectiveness of HoLEP compared with OP or two-stage TURP?

As no studies were identified reporting on the comparative effectiveness of HoLEP and two-stage TURP in the treatment of BPH in men with an expected prostate size of greater than 80-100g the cost-effectiveness of two-stage TURP was not able to be addressed here.

Time horizon: A time horizon of five years was chosen. This is based on the availability of clinical effectiveness data used in the meta-analysis presented as part of this report.

Discount rate: A discount rate of 5% was applied to all costs and effects incurred after the first year of initial treatment. The base year is 2012.

Type of economic evaluation: A cost-utility analysis was undertaken.

Economic model: A Markov model was developed, allowing patients transition through health states over the time horizon. Individual cycle lengths were six months with half-cycle correction employed to account for the continuous nature of transition probabilities within a cycle.

The model includes health states: initial treatment (with or without adverse events); well (treatment successful); long-term side effects (successful treatment but resulting in side effects); treatment failure (treatment unsuccessful requiring re-intervention); repeat treatment (with or without adverse events); treatment for urethral stricture; and death (all cause mortality).

All patients commence the model in the 'initial treatment' state.

In keeping with the DAP, patients can undergo a maximum of two HoLEP or TURP procedures over the time frame.

Treatment options after failed first procedure: The treatment options after a failed first procedure were defined in the DAP as:

Prostate size <80–100g

- Failed HoLEP: Second HoLEP or TURP

- Failed TURP: Second TURP.

Prostate size >80–100g

- Failed HoLEP: Second HoLEP, or OP

- Failed OP: no subsequent treatment option in this model.

Assumptions

Based on results of meta-analysis the length of hospital stay for treatment (without adverse events) for HoLEP, TURP and OP is two, three and five days respectively.

It was assumed that the clinical and other management of patients with BPH up to the time of procedure, as well as post-operative management are equivalent. Based on this assumption, hospital costs for HoLEP procedures were derived based on equivalent TURP costs but adjusted for lengths of stay.

For HoLEP treatment, adverse events associated with the procedure, longer-term complications and re-treatment rates were calculated by multiplying the relative risk of experiencing these events by the associated rates for TURP or OP that were derived from the meta-analysis of data.

From the published literature it was not possible to determine if a given patient experienced more than one short-term adverse event following treatment. As a result, rates of these events were derived by summing the rates presented in the meta-analysis. As the events and patient numbers that were summed are not necessarily mutually exclusive this may result in an overall over-estimation of rates. Therefore, the overall figures presented for adverse events represent a 'worst case' treatment scenario.

Adverse events associated with treatment (HoLEP or TURP) would be treated on an in-patient basis and result in additional length of hospital stay of two days. Adverse events associated with OP would be treated and resolved within the five day treatment time frame for this intervention.

Treatment for longer-term incontinence would include either behavioural interventions, including education programs and lifestyle modifications, or pharmacologic therapy using oxybutynin 5mg twice daily (or equivalent).

Treatment for urethral stricture would be performed as an in-patient procedure and undertaken by either urethrotomy or dilation. Patients would not undergo any re-treatment upon failure of initial urethral stricture treatment. The utility associated with urethral stricture is the same as that for long-term incontinence.

Transition probabilities.

Rates of short-term adverse events, longer-term side effects and re-treatment associated with TURP were derived from the meta-analysis and are shown in Table 20. All rates were transformed into probability values for use in the model using the formula:

$$P=1-e^{-rt}$$

Where P is the probability that an event will occur; e is the base of the natural logarithm; r is the rate; and t is time.

Table 20: Adverse events, urethral stricture, long-term incontinence and re-treatment values

Health state	P	Source
Adverse events (TURP)	0.18	Derived
Urethral stricture (TURP)	0.09	Derived
Long-term incontinence (TURP)	0.02	Derived
Reintervention for BPH (TURP)	0.02	Derived

The relative risk of short-term adverse events and longer-term complications including urethral stricture, incontinence and reintervention for BPH associated with HoLEP relative to TURP are shown in Table 21.

Table 21: Relative risk values of HoLEP compared to TURP

Health state	Relative Risk	95% CI	Source
Adverse events (HoLEP)	0.51	0.31 – 0.86	Derived
Urethral stricture (HoLEP)	0.65	0.33 – 1.27	Meta-analysis
Long-term incontinence (HoLEP)	0.84	0.31 – 2.28	Meta-analysis
Reintervention for BPH (HoLEP)	0.27	0.04 – 1.60	Meta-analysis

Rates of short-term adverse events, urethral stricture and long-term incontinence used in the model for OP are shown in Table 22. Similarly to TURP, these rates were transformed into probability values for use in the model as described above.

Table 22: Adverse events, urethral stricture and long-term incontinence associated with OP

Health state	*P*	Source
Adverse events (OP)	0.19	Derived
Urethral stricture (OP)	0.014	Derived
Long-term incontinence (OP)	0.05	Derived

The relative risk of adverse events, urethral stricture and long-term incontinence associated with HoLEP relative to OP are shown in Table 23.

Table 23: Adverse events, urethral stricture and long-term incontinence relative risk values of HoLEP when compared with OP

Health state	Relative Risk	95% CI	Source
Adverse events (HoLEP)	0.40	0.17 – 0.93	Derived
Urethral stricture (HoLEP)	1.07	0.30 – 3.87	Meta-analysis
Long-term incontinence (HoLEP)	0.79	0.31 – 2.04	Meta-analysis

As the model assumes that there is no failure rate for OP, the failure rate for HoLEP treatment used in the model assessing treatment in men with prostate sizes (> 80-100g) was assumed to the same as for the treatment of men with smaller prostates (<80-100g). A yearly rate of 0.003 was derived by averaging the HoLEP re-treatment rates reported in the literature (Tan 2003, Westenberg 2004). This rate was converted into a probability value as described above.

The risk of failure following treatment for urethral stricture with either urethrotomy or dilation was taken to be 0.17 (Steenkamp et al., 1997).

Costs

Costs associated with the treatment of BPH, as well as the those associated with adverse events and the treatment of any longer-term side effects stemming from the initial treatment, are summarised in Tables 24 and 25. All costs are presented in Australian dollars with the base year of 2012.

A range of proposed MBS fees for HoLEP were outlined in the DAP and were tested in the analysis. These alternate fees assess the impact of removing the tissue morcellation procedure (cost $220) from the total proposed fee, and/or the 20% premium ($200.54) over the TURP fee that was suggested by the applicant as an appropriate fee for HoLEP when morcellation is not used.

The cost for HoLEP was based on the AR-DRG costs for TURP (AR-DRG M02B). It was estimated by subtracting the direct operating room cost component of the TURP AR-DRG codes from the total cost. A per-day cost for TURP was calculated from the average length of stay. The cost of HoLEP treatment was then derived by adding the cost of two days in hospital to the MBS fee (75%) being sought for HoLEP. The 75% MBS fee rate was used in-line with the assumption that HoLEP will be performed as an in-patient procedure.

The cost for HoLEP with short-term complications was derived in a similar fashion to that described above, but using AR-DRG M02A and a length of stay of six days.

The costs for TURP treatment with and without complications were based on AR-DRG M02A and AR-DRG M02B respectively.

The cost for OP treatment was based upon the AR-DRG code for Major Male Pelvic Procedures (AR-DRG M01Z). The cost for OP treatment was estimated by subtracting the direct operating room cost component from the total AR-DRG cost. The 75% MBS fee for open prostatectomy was added to this figure to derive the cost of OP treatment.

The cost of treating urethral stricture was based on the AR-DRG code for urethral stricture (AR-DRG L66Z).

Costs for post-operative incontinence were derived on the assumptions that all patients will receive behavioural interventions funded under a referred patient treatment and management plan as the first-line treatment approach. The rate of patients not responding to behavioural interventions was estimated as 20% (Dunn and Lamb, 2009). All patients that fail behavioural interventions were assumed to receive pharmaceutical treatment of oxybutynin hydrochloride (5mg twice daily for six months).

Table 24: Source costs associated with health states used in the economic evaluation

MBS Items	Item #	100%	75%	Comments/notes
HoLEP (with morcellation)	N/A	$1,423.18	$1,067.39	Applicants suggested fee
HoLEP (with morcellation) without 20% premium	N/A	$1,222.70	$917.03	Derived from applicants suggested fee
HoLEP (excluding morcellation)	N/A	$1,203.18	$902.39	Derived from applicants suggested fee
HoLEP (excluding morcellation) without 20% premium	N/A	$1,002.70	$767.05	Taken to be the same as MBS fee for TURP
TURP	37203	$1,002.70	$767.05	
Open Prostatectomy	37200	$997.35	$748.05	
Referred patient treatment and management plan - surgery or hospital	132	$259.00	$194.25	
Referred patient treatment and management plan - surgery or hospital (follow up	133	$129.85	$97.25	

AR-DRG codes[a]	Source	Cost (total)	Cost (minus operating room component)	ALOS	Day cost (minus operating room component)
TURP with complications	AR-DRG M02A	$6,761.00	$5,725.00	7.63	$750.33
TURP without complications	AR-DRG M02B	$3,178.00	$2,332.00	3.01	$774.75
Urethral Stricture	AR-DRG L66Z	$1,275.00	N/A	N/A	N/A
Open prostatectomy	AR-DRG M01Z	$8,685.00	$5,818.00	4.87	$1,194.66

PBS Items	PBS #	Dispensed price for max qty (100 tablets).
Oxybutynin hydrochloride tablet 5 mg	8039D	$15.40

a: AR-DRG v5.1 Private Hospital Cost Weight used.

Table 25: Costs associated with health states used in the economic model

Health State Costs (Model)	Cost	Source
HoLEP treatment	$2,616.89	Derived
HoLEP with treatment adverse event	$5,569.36	Derived
TURP treatment	$3,178.00	AR-DRG M02B
TURP treatment with adverse event	$6,761.00	AR-DRG M02A
OP treatment	$6,721.35	Derived
Urethral stricture	$1,275.00	AR-DRG L66Z
Incontinence	$410.21	Derived

The health states of well and death do not have any associated costs.

Utility values

Utility values associated with the treatment of BPH were previously estimated by (Kok et al 2002) using a standard gamble technique. These were used in the analysis wherever

possible. The only instance where previously estimated values could not be used was for the health state of 'Treatment adverse event'. Utility for this health state was calculated as being pre-treatment utility minus the disutility value of 0.005 of experiencing TUR syndrome reported (Ackerman et al 2000) for two days.

Pre-treatment utility was assumed to be the same as for treatment failure.

Table 26: Utility values associated with health care states used in the economic evaluation

Health State	Utility (QALYs)	Source	Notes
Well: Treatment Successful	1	Kok et al., 2002	
Treatment adverse event	0.935	Derived	Calculated by utility of treatment failure - disutility of TUR (0.005) for 2 days
Persistent side effects	0.970	Kok et al., 2002	States of urethral stricture and long-term incontinence.
Treatment Failure	0.940	Kok et al., 2002	

Results

HoLEP in comparison with TURP – base case

The tables below summarise the base case results of the five year cost-effectiveness of various treatment pathways for BPH. Results are shown for the treatment pathways of:

1. TURP as initial treatment, followed by TURP in the event of treatment failure (comparator).

2. HoLEP as initial treatment, followed by TURP in the event of treatment failure

3. HoLEP as initial treatment, followed by a second HoLEP in the event of treatment failure.

All costs and effects are discounted at five percent per annum.

Table 27 shows the average cost per patient for each of the three strategies above. HoLEP (with HoLEP re-treatment in the event of failure) has the lowest average cost per patient of $3,095.50. Compared with the base-case treatment of TURP (with TURP re-treatment), the incremental costs associated with HoLEP (with TURP re-treatment) and HoLEP (with HoLEP re-treatment) are modelled to be $-1,395.30 and $-1,437.80 respectively.

Table 27: Modelled average cost per patient over five years of alternate treatment pathways for BPH

Strategy	Average cost per patient	Incremental Cost
TURP then TURP	$4,533.30	-
HoLEP then TURP	$3,138.00	-$1,395.30
HoLEP then HoLEP	$3,095.50	-$1,437.80

The effectiveness of each treatment pathway in terms of QALYs gained was also modelled and is shown in Table 28. The difference in QALYs between the HoLEP and TURP treatment pathways (-0.008) is minor and represents only a reduction of 2.9 days over the five year time frame of the model.

Table 28: Modelled average QALYs experienced per patient over five years of alternate treatment pathways for BPH

Strategy	QALYs	Incremental QALYs
TURP then TURP	4.499	-
HoLEP then TURP	4.491	-0.008
HoLEP then HoLEP	4.491	-0.008

Combining both the costs and effectiveness measures presented in Tables 27 and 28 allows the relative cost-effectiveness of the various treatment pathways to be evaluated. This is shown in Table 29.

Table 29: Incremental cost-effectiveness ratio of alternative treatment pathways for BPH

Strategy	Average cost per patient	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	Incremental C/E (ICER) ($/QALY)
TURP then TURP	$4,533.30	-	4.499	-	-
HoLEP then TURP	$3,138.00	-$1,395.30	4.491	-0.008	174,412.50
HoLEP then HoLEP	$3,095.50	-$1,437.80	4.491	-0.008	179,725.00

Moving treatment away from the base-case scenario of TURP (followed by TURP re-treatment) to the use of HoLEP was associated with lower treatment costs and only a marginal decrease in health outcomes. The incremental cost-effectiveness ratio (ICER) of HoLEP (followed by HoLEP) re-treatment) was $174,412.50/QALY over the HoLEP then TURP pathway and $179,725.00/QALY over the TURP then TURP pathway.

The increase in effectiveness for TURP followed by TURP pathway is counter intuitive given that it is associated with higher rates of both short and long-term adverse events as well as treatment failures. The reduction in the differences in the number of deaths in the TURP then TURP treatment pathway was found to be the cause of the minor increase in effectiveness between this treatment pathway and treatment pathways using HoLEP. They may be reasonably explained through the accumulation of rounding errors in the model as the differences in overall deaths and effectiveness is less than 1% (0.8% and 0.16% respectively). Treatment pathways using HoLEP could be considered to be at least as effective as the TURP pathway.

The figures presented above represent the average costs and QALYs associated with the various treatment pathways for BPH modelled. In order to provide a practical context on the impact that the use of different patient treatment pathways has on patient outcomes, a summary of the patient numbers experiencing key health states incorporated in the model is provided below. These numbers were derived using a hypothetical cohort of 25,000 patients with BPH with a starting age of 70 years. A starting population of 25,000

patients was selected on the basis of data from the AIHW National Hospital Morbidity Data that reports 25,252 separations for the principle diagnosis of BPH in 2007-08 (Table 30).

Table 30: Number of patients from a cohort of 25,000 that experience key modelled health states comparing the HoLEP then HoLEP and TURP then TURP treatment pathway options

Health state	HoLEP then HoLEP	TURP then TURP	Difference
Adverse events	2,400	5,221	-2,821
Urethral stricture	1,550	2,762	-1,212
Long-term incontinence	566	636	-70
Repeat procedures	1,263	4,338	-3,075
Patients successfully treated	22,325	21,583	742

It should be noted that as a single patient may experience more than one of the health states listed in the tables above throughout the five year time frame of the model (e.g. experience an adverse event but end up being successfully treated) the sum of the numbers of health states listed above can exceed 25,000.

HoLEP in comparison with TURP – sensitivity analysis

As both the accuracy and transferability of the results presented above are dependent on the accuracy of the data inputs and assumptions used in the model, a series of uni-variate and multi-variate sensitivity analyses were performed to assess the confidence that can be placed in the base case findings presented above.

Testing a range of MBS fees for HoLEP

A key assumption of the model was that the average length of stay (LOS) in hospital for HoLEP and TURP was two and three days respectively. A cost for HoLEP treatment with a three day LOS was also derived in order to assess the effect of this parameter. This cost for HoLEP was $3,391.64 compared with a corresponding cost for TURP of $3,178.00. Table 31 shows the ICERs for each treatment pathway calculated with this increased cost for HoLEP.

Table 31: Incremental cost-effectiveness ratio of alternate treatment pathways for BPH modelled with an increased cost of HoLEP associated with a three day length of hospital stay

Strategy	Average cost per patient	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	Incremental C/E (ICER) ($/QALY)
TURP then TURP	$4,533.30		4.499		-
HoLEP then TURP	$3,912.70	-$620.50	4.491	-0.008	77,575.00
HoLEP then HoLEP	$3,903.20	-$630.10	4.491	-0.008	78,762.50

These results show that even with an increased cost of HoLEP to account for an equal length of stay as TURP, the average per-patient treatment costs of the procedure are less.

The proposed MBS fee for HoLEP of $1,423.18 includes costs associated with tissue morcellation as well as an additional 20% over the fee for TURP to cover physician time required to learn the technique. A range of alternate fees, referred to in the DAP and shown in Table 24 above, were tested. Results of this assessment are presented in Table 32.

Table 32: Impact of differential MBS fees on the average treatment cost and cost-effectiveness of HoLEP treatment

Procedural costs	MBS fee (100%)	MBS fee (75%)	Average cost per patient	ICER ($/QALY) compared to TURP then TURP
HoLEP (with morcellation and 20% premium)	$1,423.18	$1,067.39	$3,095.50	179,725.00
HoLEP (with morcellation less 20% premium)	$1,222.70	$917.03	$2,938.70	199,325.00
HoLEP (excluding morcellation)	$1,203.18	$902.39	$2,923.40	201,237.50
HoLEP (excluding morcellation and 20% premium)	$1,002.70	$767.05	$2,782.30	218,875.00

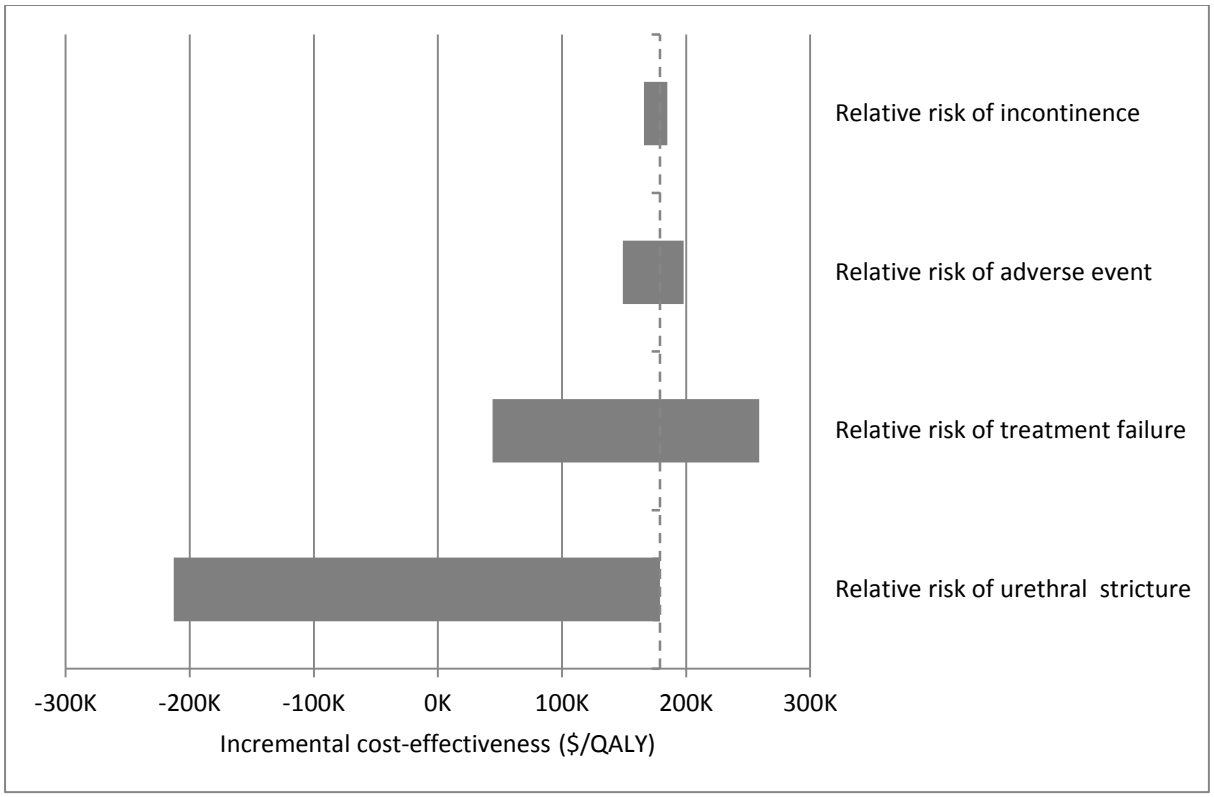
As the fee used in the base case represented the upper limit of the range of the fee tested through sensitivity analysis, the reduction in fee associated with the removal of the tissue morcellation and/or premium fee component decreased the average cost per patient in all scenarios tested.

Testing uncertainty of transition probabilities

The transition probabilities used in the economic evaluation were derived from a meta-analysis of clinical trial evidence. The probabilities of experiencing health states associated with BPH treatment using HoLEP that were used in the economic evaluation were calculated by multiplying the probability of the event occurring with TURP treatment by the relative risk associated with HoLEP treatment.

In order to test the robustness of the conclusions derived from this evaluation, sensitivity analysis was performed by multiplying the probability of an event occurring with TURP by a range of four values bound by the lower and upper limits of the 95% confidence intervals of the relative risk calculations of each event occurring with HoLEP compared with TURP. Results of this analysis comparing HoLEP and TURP treatment pathways are presented in Figure 3.

Figure 28: Sensitivity analysis comparing the HoLEP then HoLEP and TURP then TURP pathways



The base case ICER of $179,725/QALY for the HoLEP then HoLEP treatment pathway compared to TURP then TURP is represented by the dashed vertical line. This ICER varied widely when tested with through sensitivity analysis with a range of $-213,000/QALY through $259,000/QALY being obtained. The wide range of ICER values obtained is driven by the minor difference in effectiveness between the two treatment options, thus the ICER is highly sensitive to minor changes in any given parameter.

The ICER was most sensitive to changes in the relative risk of experiencing urethral stricture. Looking at this event in isolation, the ICER of HoLEP over TURP treatment from $73,724.50/QALY through to the scenario whereby HoLEP treatment was dominant over TURP due to the fact that it was both less costly and more effective than TURP treatment. HoLEP was associated with lower average per-patient treatment costs all relative risk value ranges tested (0.33 – 1.27) and only a marginal difference QALYs (4.48 – 4.52) over the five year time frame of the model.

To further test the robustness of the results of the economic evaluation a series of two-way sensitivity analyses were performed. Each parameter was tested across the 95% confidence intervals of the relative risk calculations of HoLEP compared with TURP. A range of HoLEP treatment costs associated with the different MBS fees was also tested.

Results of these sensitivity analyses showed that the treatment pathway of HoLEP then HoLEP was associated with lower average per-patient treatment costs and near equivalent effectiveness than each of the alternative treatment pathways across a wide range of conditions. The only case in which HoLEP then HoLEP treatment may not be as cost-effective as alternative treatment pathways was when both the upper limits of the

cost of HoLEP treatment and treatment failure rates for HoLEP were tested. In this instance the treatment pathway of TURP then TURP was more favourable. As there is very wide range of the 95% confidence intervals around the relative risk of the HoLEP treatment failure compared to TURP, and that TURP followed by TURP is only cost-effective when the upper bounds of the risk of HoLEP treatment failure are experienced, treatment pathways employing HoLEP remain acceptable across all but the most extreme scenarios.

HoLEP in comparison with OP – base case

The tables below summarise the base case results of the five year cost-effectiveness of various treatment pathways for BPH in men with expected prostate sizes >80-100g. Results are shown for the treatment pathways of:

1. OP as initial treatment, no second treatment available (comparator)

2. HoLEP as initial treatment, followed by OP upon treatment failure

3. HoLEP as initial treatment, followed by a second HoLEP upon treatment failure.

All costs and effects are discounted at five percent per annum.

Table 33 shows the average cost per patient for each of three strategies above. HoLEP (with HoLEP re-treatment in the event of failure) has the lowest average cost per patient of $2,905.40. Compared with the base-case treatment of OP, the incremental costs associated with HoLEP (with OP re-treatment) and HoLEP (with HoLEP re-treatment) are modelled to be $-3,814.50 and $-3,854.60 respectively.

Table 33: Modelled average cost per patient over five years of alternative treatment pathways

Strategy	Average cost per patient	Incremental Cost
OP	$6,760.00	-
HoLEP then OP	$2,945.50	-$3,814.50
HoLEP then HoLEP	$2,905.40	-$3,854.60

The effectiveness of each treatment pathway in terms QALYs gained was also modelled and this is shown in Table 34. It should be noted that the difference in QALYs between treatment pathways (~0.006) is very minor and represents only an additional 2.2 days of full health over the five year time frame of the model.

Table 34: Modelled average QALYs experienced per patient over five years of alternate treatment pathways

Strategy	QALYs	Incremental QALYs
OP	4.46018	
HoLEP then OP	4.46655	0.00637
HoLEP then HoLEP	4.46655	0.00636

Combining both the costs and effectiveness measures presented in Tables 33 and 34 allows the relative cost-effectiveness of the various treatment pathways to be evaluated. This is shown in Table 35.

Table 35: Incremental cost-effectiveness ratio of alternate treatment pathways

Strategy	Average cost per patient	Incremental Cost	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	Incremental C/E (ICER) ($/QALY)
OP	$6,760.00	-	4.46018	-	-
HoLEP then OP	$2,945.50	-$3,814.50	4.46655	0.00637	-598,822.61
HoLEP then HoLEP	$2,905.40	-$3,854.60	4.46655	0.00636	-605,117.74

The treatment pathways of HoLEP then HoLEP and HoLEP then OP were both found to dominate that of OP in that they were less costly and more effective. The primary driver of the high ICER figures obtained is that there is only a modest increase in effectiveness in the treatment pathways using HoLEP. From a practical standpoint, these two treatment options may be considered equivalent.

The figures presented above represent the average costs and QALYs associated with the various treatment pathways for BPH modelled. In order to provide a practical context on the impact that the use of different patient treatment pathways has on patient outcomes, Table 36 presents a summary of the patient numbers experiencing key health states in either the HoLEP or OP pathways is provided below. As with the economic evaluation of HoLEP in comparison with TURP above, these numbers were derived using a hypothetical cohort of 25,000 patients with BPH with a starting age of 70 years.

Table 36: Number of patients from a cohort of 25,000 that experience modelled health states comparing the HoLEP then HoLEP and OP treatment pathway options

Health state	HoLEP (followed by HoLEP)	OP	Difference
Adverse events	1,918	4,750	-2,832
Urethral stricture	265	250	15
Long-term incontinence	1,005	1,251	-246
Repeat procedures	309	0	309
Patients successfully treated	22,630	22,666	-36

A single patient may experience more than one of the health states listed in Table 36 above throughout the five year time frame of the model (e.g. experience an adverse event but end up being successfully treated), thus the sum of the numbers of health states listed above can exceed 25,000.

The figures presented in Tables 36 show that treatment with HoLEP (then HoLEP) is associated with fewer patients experiencing an adverse event associated with treatment, or suffering from long-term incontinence. As treatment failure was not an option following OP, both treatment pathways with this option resulted in more patients being successfully treated.

HoLEP in comparison with OP – sensitivity analysis

As both the accuracy and transferability of the results presented above are dependent on the accuracy of the data inputs and assumptions used in the model, a series of uni-variate and multi-variate sensitivity analyses were performed to assess the confidence that can be placed in the base case findings presented above.

Testing a range of MBS fees for HoLEP

A key assumption of the model was that the average LOS for HoLEP and OP was two and five days respectively. A cost for HoLEP treatment with a three day LOS was derived. This cost was $3,391.64 compared with a corresponding cost for OP of $6,761.00. Table 37 shows the ICERs for each treatment pathway calculated with this increased cost for HoLEP.

Table 37: ICER of three day HoLEP length of stay in comparison to OP

Strategy	Average cost per patient	Incremental Cost (from HoLEP then HoLEP)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	Incremental C/E (ICER) ($/QALY)
OP	$6,760.00	-	4.46018	-	-
HoLEP then OP	$3,720.20	-$3,039.70	4.46655	0.00637	-477,205.65
HoLEP then HoLEP	$3,688.20	-$3,071.70	4.46655	0.00636	-482,229.20

Results presented in Table 37 show that even with an increased cost of HoLEP to account for an additional length of stay in hospital of one day that the average per-patient treatment cost of the treatment option of HoLEP remained less than either pathway with OP and that strategies employing HoLEP were dominant over OP.

A sensitivity analysis testing a range of MBS fees for HoLEP excluding the tissue morcellation and/or premium component was performed for OP in the same fashion as TURP (Table 38).

Table 38: Impact of different MBS fees on the average treatment cost and cost-effectiveness of HoLEP treatment

Procedural costs	MBS fee (100%)	MBS fee (75%)	Average cost per patient	ICER ($/QALY) compared to OP
HoLEP (with morcellation and 20% premium)	$1,423.18	$1,067.39	$2,905.40	-605,117.74
HoLEP (with morcellation less 20% premium)	$1,222.70	$917.03	$2,753.50	-629,434.85
HoLEP (excluding morcellation)	$1,203.18	$902.39	$2,738.70	-631,287.28
HoLEP (excluding morcellation and 20% premium)	$1,002.70	$767.05	$2,601.90	-652,762.95

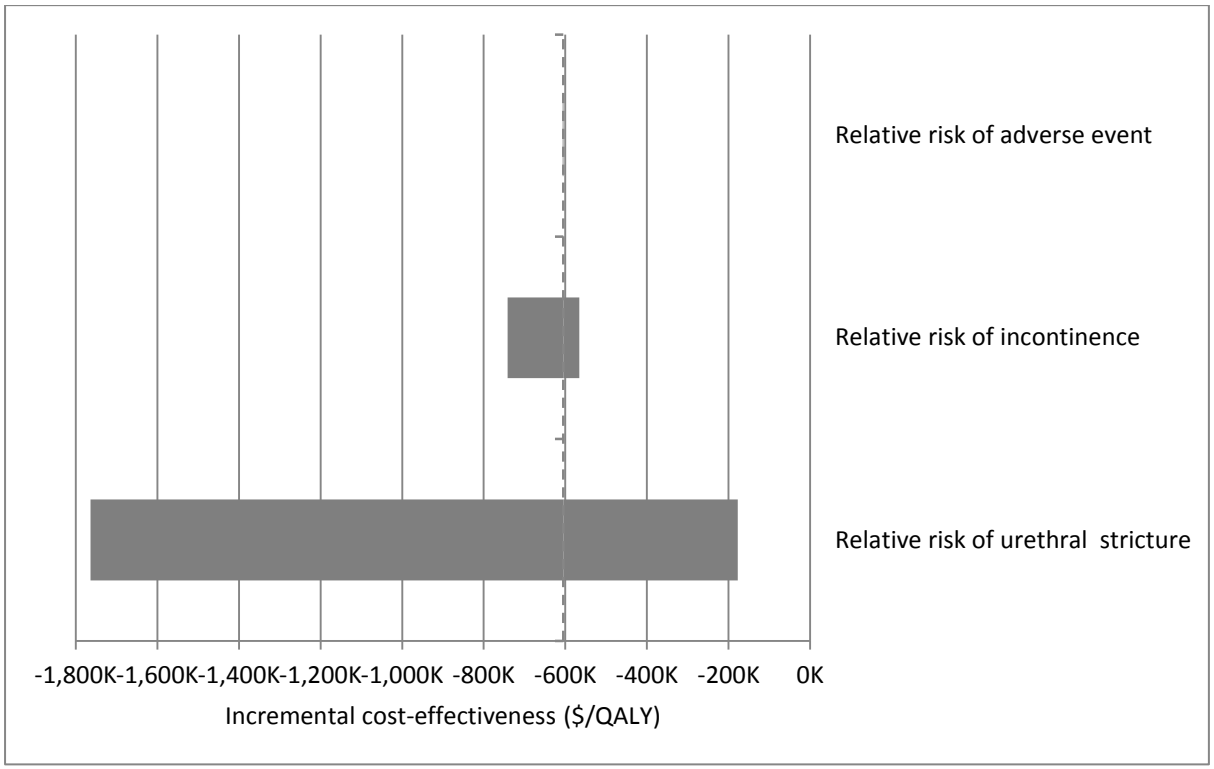
Testing uncertainty of transition probabilities

The transition probabilities used in the economic evaluation were derived from a meta-analysis of clinical trial evidence. The probabilities of experiencing health states associated with BPH treatment using HoLEP that were used in the economic evaluation

were calculated by multiplying the probability of the event occurring with OP treatment by the relative risk associated with HoLEP treatment.

In order to test the robustness of the conclusions derived from this evaluation, sensitivity analysis was performed by multiplying the probability of an event occurring with OP by a range of four values bound by the lower and upper limits of the 95% confidence intervals of the relative risk calculations of each event occurring with HoLEP compared with OP (refer to Table 23). Results of this analysis comparing HoLEP and TURP treatment pathways are presented in Figure 6.

Figure 29: Sensitivity analysis comparing the HoLEP then HoLEP and OP treatment pathways



The vertical dashed line represents the base case ICER (-$605,117/QALY). For the treatment pathway of HoLEP then HoLEP compared to OP, the strategy employing HoLEP as the primary treatment option remained dominant across all variables tested in that HoLEP treatment was both less and more effective than OP.

To further test the robustness of the results of the economic evaluation a series of two-way sensitivity analyses was performed. In regards to rates of key parameters used in the model, each parameter was tested across the 95% confidence intervals of the relative risk calculations of HoLEP compared with OP. A range of HoLEP treatment costs incorporating the MBS fees presented in Table 24 as part of the overall treatment costs was also tested.

Results of these sensitivity analyses showed that the treatment pathway of HoLEP then HoLEP was more cost-effective than both the HoLEP then OP and OP treatment pathways across all variables tested (data not shown).

Comments in relation to economic evaluation

Prostate size <80–100g

In both economic evaluations HoLEP treatment was demonstrated to be associated lower average per-patient treatment costs then treatment options including either TURP or OP, with very similar health utility values. This lower cost is driven by the reduced length of stay required for HoLEP treatment, as well as reduced rates of adverse events, long-term incontinence and treatment failure.

In regards to the treatment of BPH in men with expected prostate sizes <80-100g, the treatment pathway of HoLEP followed by a second HoLEP upon initial treatment failure was found to be less costly with only a marginal difference in effectiveness across a wide range of variables tested through sensitivity analysis. A treatment approach that used TURP as a second procedure was found to be favourable when the treatment failure rates for HoLEP approach the upper bounds of the 95% confidence interval for the relative risk of treatment failure of HoLEP compared to TURP. There here is a wide 95% confidence interval (0.04 – 1.60) around the relative risk of HoLEP treatment stemming from a paucity of literature that explicitly reported on this outcome in comparison to other parameters explored in the economic evaluation. Thus, there is increased uncertainty surrounding this parameter than others tested in this evaluation.

When treatment pathways of HoLEP then HoLEP and TURP then TURP were compared, HoLEP treatment was associated with lower average per-patient costs that TURP treatment with only a negligible difference in effectiveness (-0.008 QALYs). As described previously, the origin of this difference in effectiveness is an artefact of the calculation of patient progression through the model and the two treatment pathways may be considered equally effective but with lower treatment cost being associated with HoLEP. If the difference in effectiveness is taken into account the use of HoLEP over TURP results in an ICER of $179,293/QALY with the higher ICER being driven by the marginal difference in effectiveness between treatment approaches.

Prostate size >80–100g

The treatment pathway employing HoLEP followed by a second HoLEP upon initial treatment failure was found to have a lower average per-patient cost with superior effectiveness to treatment pathways employing OP. The reduction of cost was primarily driven by a reduced cost of treatment as a result of HoLEP requiring a reduced LOS than OP. When the costs associated with a LOS for HoLEP were adjusted upwards from two to three days HoLEP treatment remained a more cost-effective strategy.

The treatment pathway of HoLEP then HoLEP remained preferable to that of HoLEP then OP or OP alone across all conditions tested through sensitivity analysis.

Whilst associated with few instances of repeat procedures (assumed to be zero), the avoidance of costs associated with the need to repeat a number of HoLEP procedures was not offset by the initially higher treatment costs (additional $4,104.46) associated with OP, as well as costs associated with increased rates of adverse events and long-term incontinence.

It should be noted that the inputs used in the economic evaluation assessing the treatment of BPH in men with an expected prostate size >80-100g were only based upon data published in two clinical trials (Kuntz 2008, Naspro 2006) that enrolled 120 and 80 patients respectively. This differs from the evaluation assessing the comparative effectiveness of HoLEP and TURP treatment in men with an expected prostate size of <80-100g that was based on evidence derived from seven studies. As a result of this difference in the body of evidence informing the comparative effectiveness of HoLEP, whilst the evidence at hand suggests that HoLEP is a cost-effective treatment option for BPH compared to OP, some caution should be exercised in drawing firm conclusions from the assessment provided in this report. This uncertainty regarding the comparative cost-effectiveness of HoLEP treatment compared with OP was reflected in the wide range of values obtained from the conduct of sensitivity analysis. However given that HoLEP treatment was consistently found to be associated with a lower average per-patient treatment cost, and superior effectiveness, the availability of more data could be anticipated to reduce this uncertainty rather than alter the outcome of the assessment.

Financial implications

The number of men who undergo surgical treatment for BPH annually in Australia was shown in Table 6, page 4. It indicates that the number of separations for a principal diagnosis of BPH rose slightly from approximately 21,000 in 1998-1999 to approximately 25,000 in 2005-2006. There have been approximately 25,000 separations for this diagnosis each year since then, and the last years of available figures are 2009-2010.

The number of occurrences of the principal procedures used to treat BPH in the year 2007-2008 was obtained from the AHIW National Hospital morbidity data using the Australian Classification of Health Interventions (ACHI) codes for procedures. These are shown in Table 39 below.

Table 39: Occurrences for principal procedures to treat BPH 2007-2008

ACHI (5th edn)		Procedure	Occurrences (2007-08)
1165 Transuretheral prostatectomy	37201-00	Transurethral needle ablation of prostate [TUNA]	64
	37203-00	Transurethral resection of prostate [TURP]	21963
	37203-02	Transurethral electrical vaporisation of prostate	36
1166 Other closed prostatectomy	37203-03	Cryoablation of prostate	25
	37203-05	High intensity focused ultrasound [HIFUS] (transrectal) of prostate	68
	37203-06	Other closed prostatectomy	491
	37207-00	Endoscopic laser ablation of prostate	317
	37207-01	Endoscopic laser excision of prostate	323
1167 Open prostatectomy	37200-03	Suprapubic prostatectomy	59
	37200-04	Retropubic prostatectomy	99
	37200-05	Other open prostatectomy	212

Source: AIHW National Hospital Morbidity Database

These data would indicate that approximately 22,000 TURP and 370 OP procedures were undertaken across public and private hospitals in the year 2007-2008.

The requested Medicare items processed for surgical treatments for BPH from July 2007 to June 2010 are shown in Table 40.

Table 40: Requested Medicare items processed from June 2007 to June 2010

MBS Item Number	Procedure	Fee	2007/08	2008/09	2009/10
37203	Transurethral resection of prostate [TURP]	$1,002.70	12,158	12,557	12,690
37207	Visual laser ablation	$833.65	319	460	699
37224	Diathermy or visual laser destruction	$310.95	240	249	232
37200	Open Prostatectomy	$977.80	141	153	142
37206	Transurethral resection of prostate [TURP] (continuation within 10 days)	$536.95	24	30	33
37230	Transurethral microwave thermotherapy [TUMT]	$1,002.65	59	62	28
37201	Transurethral needle ablation [TUNA]	$797.45	37	17	13
37208	Visual laser ablation (continuation within 10 days)	$400.30	2	2	2
37202	Transurethral needle ablation [TUNA] (continuation within 10 days)	$400.30	3	1	1
37233	Transurethral microwave thermotherapy [TUMT] (continuation within 10 days)	$536.95	1	0	1

Source: Medicare Australia Statistics

These Medicare statistics provide a guide as to the relative casemix of these procedures. Whereas AIHW data records separations in both public and private hospitals in Australia, the Medicare items processed provide a guide as to the number of procedures that are performed outside of inpatient public hospital treatment. They therefore provide a guide to the potential direct costs to the government.

The increased Medicare item fee proposed for HoLEP ($1,423.18) compared with TURP ($1,002.70) or OP ($977.80) means that, if MBS listed, there will be increased direct costs to government where the new procedure is carried out. Indirect cost savings that may accrue as a result of any shorter length of stay associated with the procedure or as a result of reduced complications would be realised by hospitals providing the procedure, by health insurers or by the patients.

Estimates of the likely uptake of HoLEP as a replacement procedure for either TURP or HoLEP are difficult to make. It is noted in the DAP that due to the training requirements to develop skills in the procedure, uptake would initially be low and would increase gradually over time. It states that the procedure would be undertaken by trained urologists with the assistance of nursing staff and an anaesthetist. There is a learning curve to develop skills in the procedure which would require considerable investment from individual urologists in terms of both time and money. Therefore, HoLEP would be undertaken in specialist urology centres by specially trained urologists.

In relation to HoLEP, the applicant estimated in their submission that 5-15% of the annual number of TURP cases might be considered "high-risk". Patients would include those with cardiac conditions or those on anti-coagulant medication. HoLEP would in these patients be a suitable alternative. The procedure might also be expected to replace OP, due to the more invasive nature of the latter.

The projected number of HoLEP MBS item claims that may occur on an annual basis over a five year period is estimated in Table 41 below. It is based on a number of assumptions including:

- The incidence rate and total populations of men with BPH remains relatively constant, so that the total number of surgical procedures required for the condition also remain at current levels.
- The costs of the individual procedures are assumed to be stable over the period.
- HoLEP would be an alternative to either TURP or OP only in this time frame. It is not expected, for example, that HoLEP would affect other procedures such as visual laser treatment numbers.
- These estimates assume a growth rate of HoLEP that is equivalent with 5% of the total number of existing TURP procedures by year 3, and a rate of 10% by year 10. This is in line with the applicant's estimates and is broadly equivalent to the current utilisation of visual laser ablation options. This growth rate may be conservative but takes into account the need for surgeon training, capital investment and business planning in the event of a positive MBS listing.
- Five percent of the total number of current OPs that are performed are converted to HoLEP. It is unclear whether this is an over or an under-estimate, although the total numbers are small.

Table 41: Projected numbers of MBS item claims from 2013-2017 in event of positive HoLEP listing

	2012	2013	2014	2015	2016	2017
		Year 1	Year 2	Year 3	Year 4	Year 5
TURP procedures	12,500	12,375	12,125	11,875	11,875	11,250
OP procedures	150	137	137	137	137	137
HoLEP procedures replacing TURP	-	125	375	625	625	1,250
HoLEP procedures replacing OP	-	13	13	13	13	13
Total HoLEP procedures	-	138	388	638	638	1,263
Total number of BPH procedures	12,650	12,650	12,650	12,650	12,650	12,650

Based on the projected numbers above, the total MBS cost over the five years is shown in Table 42 below.

The total costs of the MBS item fees over a five year period based on the above numbers are shown in Table 42 below. They show the additional costs that would be incurred each year associated with the listing of HoLEP as well as the total cost to Government given that there would only be a 75% benefit on these items.

Table 42: Total cost over a five year period

	Item fee	2012	2013	2014	2015	2016	2017
			Year 1	Year 2	Year 3	Year 4	Year 5
TURP procedures		12,500	12,375	12,125	11,875	11,875	11,250
OP procedures		150	137	137	137	137	137
HoLEP procedures (total)		-	138	388	638	638	1,263
TURP MBS fees	$1,002.70	$12,533,125	$12,407,794	$12,157,131	$11,906,469	$11,906,469	$11,279,813
OP MBS fees	$977.80	$146,670	$133,958	$133,958	$133,958	$133,958	$133,958
HoLEP MBS fees	$1,423.18	$-	$196,398	$552,193	$907,988	$907,988	$1,797,476
Total MBS fees for BPH procedures over 5 years		$12,679,795	$12,738,151	$12,843,284	$12,948,416	$12,948,416	$13,211,247
Additional costs each year associated with HoLEP listing		$-	$58,356	$163,488	$268,621	$268,621	$531,452
Total additional cost to Government (75%)		**$-**	**$43,767**	**$122,616**	**$201,465**	**$201,465**	**$398,589**

The table below shows the corresponding figures in the event that HoLEP were listed at $1,202.18 i.e. without morcellation.

Table 43: Total cost over a five year period without morcellation

	Item fee	2012	2013	2014	2015	2016	2017
			Year 1	Year 2	Year 3	Year 4	Year 5
TURP procedures		12,500	12,375	12,125	11,875	11,875	11,250
OP procedures		150	137	137	137	137	137
HoLEP procedures (Total)		-	138	388	638	638	1,263
TURP MBS fees	$1,002.70	$12,533,125	$12,407,794	$12,157,131	$11,906,469	$11,906,469	$11,279,813
OP MBS fees	$977.80	$146,670	$133,958	$133,958	$133,958	$133,958	$133,958
HoLEP MBS fees (excluding morcellation)	$1,423.18	-	$196,398	$552,193	$907,988	$907,988	$1,797,476
Total MBS fees for BPH procedures over 5 years		$12,679,795	$12,738,151	$12,843,284	$12,948,416	$12,948,416	$13,211,247
Additional costs each year associated with HoLEP listing			$58,356	$163,488	$268,621	$268,621	$531,452
Total cost to Government (75%)			**$43,767**	**$122,616**	**$201,465**	**$201,465**	**$398,589**

The tables above indicate that the projected annual additional costs to the Government range are predicted to range from $43,767 in year 1 to $398,589 in year 5, based on the

assumptions described above. The equivalent ranges in the event of HoLEP listing at the reduced fee (without morcellation) range from $20,893 in year 1 to $189,247.

It should be noted that the figures above do not take into account the number of HoLEP procedures that might be undertaken in a public hospital. The total number of HoLEP procedures being performed annually over the five year period may also be greater than the numbers projected in the tables and which will be dependent on the availability of trained surgeons to undertake them and investment by the institution.

Discussion

The assessment of HoLEP as a potential new publicly funded surgical procedure for the treatment of men with benign prostatic hyperplasia throughout this report was based on a direct comparison with either TURP or OP.

Is it safe?

The evidence from systematic reviews and RCTs reviewed in this report indicates that HoLEP is a relatively safe procedure when compared with either TURP or OP procedures. Safety outcomes listed in the DAP and others identified in the literature reviewed include blood transfusion rates post-procedure, urethral stricture, incontinence, TUR syndrome, erectile dysfunction, dysuria, capsular perforation as well as overall mortality.

The evidence from the systematic review and subsequent RCTs that informed the comparison of HoLEP with TURP indicated that HoLEP offers statistically significant advantages over TURP in respect of blood transfusion rates post procedure. This evidence includes data from seven RCTs in total with 348 patients randomised to HoLEP and 342 randomised to TURP. Non-significant differences between the two were observed for all of the other outcomes considered.

HoLEP also appears to be as safe as OP across the range of outcomes assessed, although this information is analysed from fewer studies and with a smaller number of patients. In a meta-analysis of the two studies, patients allocated to HoLEP were less likely to have a blood transfusion than those allocated to TURP. This evidence includes data from two RCTs in total in which 101 patients were randomised to HoLEP and 99 to OP. Other complications, such as incontinence and stricture, were comparable between the groups.

Is it effective?

The body of evidence included in this assessment was appraised according to the NHMRC guidelines (NHMRC 2009), which are summarised under 'Assessment of the body of evidence' on page 20.

HoLEP compared with TURP

The evidence base for the assessment of HoLEP in comparison to TURP is based on seven RCTs. Five of these were included in a systematic review, and this has been updated with two more recent RCTs identified as part of this assessment. In these studies348 patients have been treated with HoLEP and 342 patients treated with TURP. The RCTs included in this assessment did not give adequate details of either the random allocation and allocation concealment of patients in the trials. This lack of detail is not uncommon in surgical trials(McCulloch et al 2002). It does however mean that the trials are assessed at having a high or unclear risk of bias. Only one trial (Tan 2003) reported that outcome assessors were blinded to treatment allocation (cited in Lourenco et al 2008). Functional outcomes such as Qmax and PVR are not influenced by lack of blinding. Symptom scores (IPSS/AUA) and quality of life measures may however be impacted.

Functional outcomes are consistent across the studies (with the exception of Qmax at six months). Pooling of the results for both symptom scores and quality of life measures indicates substantial heterogeneity – this may be explained by the lack of blinding of assessors. The assessment of symptom scores across the studies from 12 months, to a follow-up to 92 months, indicates that patients treated with HoLEP had lower symptom scores in comparison to patients in the TURP group. These differences were not however significant. There were no significant differences in quality of life data. Inconsistencies in relation to the duration of operation can be expected given the high level of specialisation and skills required. Surgeon experience was frequently not reported in the trials. It is difficult to know the impact of this experience in relation to the results reported.

The primary outcomes assessed in the trials are those that were listed in the DAP. Bother scores, included in the protocol, were not reported in the any of the studies. The longest follow-up reported was at 92 months. Some significant differences in outcomes between patients treated with HoLEP in comparison with TURP were reported; although at two years most of the differences were not significant. However, patients treated with HoLEP tended to have better outcomes.

The clinical flowcharts indicate that men treated with HoLEP (or another surgical treatment) should be those with moderate to severe symptomatic BPH (based on symptom score) in whom active surveillance, conservative treatment and medical management have failed or are inappropriate. The inclusion criteria of the trials varied. Lourenco et al for example reports that its five RCTs 'provided details of the participants' IPSS/AUA symptom scores and prostate size, showing that all 580 participants had severe symptoms and large prostates at trial entry' (p65). It is not indicated however whether specific symptom scores were used as cut-offs for patient eligibility, or whether patients had previously failed to respond to pharmaceutical treatment. Mavuduru et al's inclusion criteria stipulated only that patients be eligible for surgery for symptomatic BPH (2009). Eltabey et al's inclusion criteria stipulated that patients have bladder outlet obstruction caused by BPH, related voiding symptoms, prostate size between 30–100g, had not responded to pharmacologic therapy, were eligible for surgical treatment, and had a specific AUA score and Qmax (2010).

No published Australian studies were identified. The studies by Tan (2003) (follow-up to Wilson et al 2006 and Gilling et al 2011) and Westenberg et al (2004) were from a high-volume HoLEP centre in New Zealand. Clinical advice indicates that this is very similar to an Australian population and practice.

The body of evidence assessment matrix for the comparison of HoLEP and TURP is shown in Table 44.

Table 44: Completed body of evidence assessment matrix; HoLEP versus TURP

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability		Population/s studied in the body of evidence are similar to the target population		
Applicability			Probably applicable to Australian healthcare context with some caveats	

HoLEP compared with OP

Two RCTs(comprising in total 101 patients treated with HoLEP and 99 patients treated with OP) were included in this comparison. Both RCTS had an unclear risk of bias due to the lack of details provided in regards to randomisation and allocation concealment as well as blinding of personnel and outcome assessors. It is difficult to know whether this is an issue of poor reporting of methods or a reflection of studies with a high risk of biases.

These studies were consistent in that both reported similar results in respect to HoLEP and OP. No heterogeneity was observed in pooling the results, although this is only based on two studies.

With regards to clinical impact no significant differences between the procedures were noted. All outcomes were comparable, with a maximum follow-up of 60 months. All primary outcomes in the DAP were reported in the trials (with the exception of bother scores, not reported in either study).

The clinical flowcharts indicate that men treated with HoLEP (or another surgical treatment) should be those with moderate to severe symptomatic BPH (based on symptom score) in whom active surveillance, conservative treatment and medical management has failed or is inappropriate. The inclusion criteria of the trials varied. One study included patients in whom pharmacologic therapy had failed, and where BPH was based on functional outcomes such as post void residual volume rather than symptom scores. In the second study symptom score was used as an inclusion criteria. It was unclear however whether patients had previously undergone, and not responded to, conservation and medical treatment. In this study patients also had a prostate larger than 100g.

No Australian studies were identified. The RCTs were from single centres in Europe (Germany and Italy).

The body of evidence assessment matrix for the comparison of HoLEP and OP is shown in Table 45.

Table 45: Completed body of evidence assessment matrix: HoLEP versus OP

Body of evidence / Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact			Moderate	
Generalisability			Population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	
Applicability			Probably applicable to Australian healthcare context with some caveats	

Adapted from (NHMRC 2009).

Conclusions

Safety

HoLEP appears to be as safe as TURP across the range of outcomes assessed. There would appear to be statistically significant advantages over TURP in relation to blood transfusion rates post procedure. The evidence from the systematic review and two additional RCTs that update it suggests that differences in the rates of other adverse events are not statistically significant. Some caution should be exercised in the interpretation of this information given the wide confidence intervals that exist around some of the outcomes.

HoLEP also appears to be as safe as OP across the range of outcomes assessed, although this information is analysed from fewer studies and with a smaller total number of patients. In a meta-analysis of the two studies, patients allocated to HoLEP were less likely to have a blood transfusion than those allocated to OP. Other complications, such as incontinence and stricture, were comparable between the groups

Effectiveness

HoLEP appears to be as effective, or more effective, than TURP across a range of effectiveness outcomes. These include peak flow (Qmax), symptom scores and PVR. Caution should however be exercised in the interpretation of these findings given wide confidence intervals and significant heterogeneity across the studies. Quality of life differences and differences between the two interventions in respect of treatment failure/re-treatment rates were not significant.

A HoLEP procedure takes longer to complete than a TURP procedure, but is associated with a statistically significant shorter hospital stay. Catheterisation times are also shorter. Surgeon experience was often not noted in the studies and so it difficult to ascertain whether these results would reflect current operative times.

There is a satisfactory evidence base for this comparison of HoLEP and TURP, with several RCTs providing consistent evidence. This evidence is considered to be generalisable given that the patients included in these studies are likely to be similar to those for whom treatment is envisaged in Australia.

HoLEP appears to be as effective as OP across a range of effectiveness outcomes, albeit with a smaller body of evidence. These include Qmax, symptom scores and PVR. No evidence of superiority for HoLEP (or OP) was demonstrated.

A HoLEP procedure also may take longer to complete than an OP procedure, but may be associated with a shorter hospital stay and shorter catheterisation times.

The evidence base for the comparison of HoLEP and OP is limited to two RCTs with 100 patients in total in each arm. Results from these trials are consistent, and are probably still generalisable to the Australian population.

Economic considerations

Economic modelling to assess the costs and effects of various treatment options for BPH was undertaken. The economic evaluations undertaken showed that HoLEP treatment was associated with lower average per-patient treatment costs than treatment options including either TURP or OP, with very similar effectiveness. This lower cost is driven by the reduced length of stay required for HoLEP treatment, as well as reduced rates of adverse events, long-term incontinence and treatment failure.

TURP as the comparator

When treatment pathways of HoLEP (with HoLEP for re-treatment if necessary) and TURP (with TURP for re-treatment) were compared, HoLEP was associated with lower average per-patient costs than TURP treatment with only a negligible difference in effectiveness (-0.008 QALYs). The origin of this difference in effectiveness is an artefact of the calculation of patient progression through the model and the two treatment pathways may be considered equally effective. There were lower treatment costs associated with HoLEP.

There was only a marginal difference in effectiveness across a wide range of variables tested through sensitivity analysis.

OP as the comparator

The treatment pathway employing HoLEP followed by a second HoLEP upon initial treatment failure was found to have a lower average per-patient cost with superior effectiveness to treatment pathways employing OP. The reduction of cost was primarily driven by a reduced cost of treatment as a result of HoLEP requiring a reduced LOS than OP. When the costs associated with a LOS for HoLEP were adjusted upwards from two to three days HoLEP treatment remained a more cost-effective strategy.

The treatment pathway of HoLEP then HoLEP remained preferable to that of HoLEP then OP or OP alone across all conditions tested through sensitivity analysis.

It should be noted that the inputs used in the economic evaluation assessing the treatment of BPH in men with an expected prostate size >80-100g using either HoLEP or OP was only based upon data published in two clinical trials with 200 patients in total. Thus, whilst the evidence at hand suggests that HoLEP is a cost-effective treatment option for BPH compared to OP, some caution should be exercised in drawing firm conclusions from the assessment provided in this report. This uncertainty regarding the comparative cost-effectiveness of HoLEP treatment compared with OP was reflected in the wide range of values obtained from the conduct of sensitivity analysis. However, given that HoLEP treatment was consistently found to be associated with a lower average per-patient treatment cost, and superior effectiveness, the availability of more data could be anticipated to reduce this uncertainty rather than alter the outcome of the assessment.

Costing

There is a learning curve to develop skills in the procedure. It is likely therefore that uptake of the procedure following positive listing would initially be slow, and increase gradually over time. Estimates of uptake of the procedure over a five year period in the event of a positive listing ranged from 1% of the total number of TURP procedures that are performed annually by year 1 and rising to 10% by year 5.

The listing of HoLEP would have an additional direct cost to the MBS on an annual basis as a result of the increased fee for the item. The indirect cost savings that occur – through reduced length of stay and reduced complications – would accrue to hospitals, to health insurers and to patients.

Based on the projections outlined in this assessment, it is estimated that the additional cost to the MBS as a result of positive listing of this procedure would be $201,465 by year 3 and rising to $398,589 by year 5. These costs reflect only the 75% benefit for the item and it is expected that any additional costs would be out-of-pocket.

Appendix A Health Expert Standing Panel and Assessment Group

Application 1149 – Holmium:YAG laser enucleation of the prostate (HoLEP) for the treatment of benign prostatic hyperplasia

Medical Expert Standing Panel

Member	Expertise or Affiliation
Dr Nader Awad FRACS (UROL) Senior Lecturer UNSW, UNE, NU	Senior Urologist. Head of Department Port Macquarie.
Dr Andrew Tan Royal Perth Hospital/Mount Private Hospital Western Australia	Consultant Urological Surgeon

Assessment Group

Name	Organisation
Anna Stoklosa	NHMRC Clinical Trials Centre, University of Sydney
Sally Wortley	NHMRC Clinical Trials Centre, University of Sydney
Toby Gould	NHMRC Clinical Trials Centre, University of Sydney
Samara Lewis	NHMRC Clinical Trials Centre, University of Sydney
Martin Flattery	NHMRC Clinical Trials Centre, University of Sydney

Appendix B Search strategies

#	**Embase**
1	'prostate hypertrophy'/exp OR 'prostate hypertrophy'
2	bph:ab,ti
3	bpo:ab,ti
4	bpe:ab,ti
5	(prostat* NEXT/3 hyper*):ab,ti
6	benign:ab,ti AND (prostat* NEXT/3 (enlarge* OR obstruct* OR disease)):ab,ti
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	'holmium laser':ab,ti
9	'yag laser':ab,ti
10	(laser NEAR/3 (enucleat* OR prostatect* OR resect* OR ablat*)):ab,ti
11	holep:ab,ti
12	#8 OR #9 OR #10 OR #11
13	#7 AND #12
14	'randomized controlled trial'/exp OR 'randomized controlled trial'
15	'randomization'/exp OR randomization
16	'randomi?ed controlled trial$':ab,ti
17	rct:ab,ti
18	'random allocation':ab,ti
19	'randomly allocated':ab,ti
20	#14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#13 AND #20
22	#13 AND #20 AND [2006-2012]/py
23	'review'/exp OR review
24	medline:ab,ti
25	#23 AND #24
26	'meta-analysis'/exp OR 'meta-analysis'
27	systematic*:ti,ab AND (review$ or overview$):ti,ab
28	meta?analy$:ab,ti
29	meta analy*:ab,ti
30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
31	#30 AND #13
32	#30 AND #13 AND [2006-2012]/py
33	‘socioeconomics’/de
34	'cost benefit analysis'/de
35	'cost-effectiveness analysis'/de
36	'cost of illness'/de
37	'cost control'/de
38	'economic aspect'/de
39	'financial management'/de
40	'health care cost'/de

41	'health care financing'/de
42	'health economics'/de
43	'hospital cost'/de
44	(fiscal or financial or finance or funding):ab,ti
45	'cost minimization analysis'/de
46	(cost NEAR/1 estimate$):ab,ti
47	(cost NEAR/1 variable):ab,ti
48	(unit NEAR/1 cost$):ab,ti
49	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
50	#49 AND #13
51	#49 AND #13 AND [2006-2012]/py
52	#22 OR #32 OR #51

#	**PreMedline**
1	exp prostatic hyperplasia/
2	BPH.mp
3	BPO.mp
4	BPE.mp
5	(prostat* adj3 hyper*).tw
6	benign.tw AND (prostat* adj3 (enlarge* OR obstruct* OR disease)).tw
7	1 or 2 or 3 or 4 or 5 or 6
8	holmium laser.tw
9	yag laser.tw
10	(laser adj3 (enucleat* or prostatect* or resect* or ablat*)).tw.
11	holep.tw
12	8 or 9 or 10 or 11
13	7 and 12
14	Randomized controlled trial.pt
15	Controlled clinical trial.pt
16	Randomized.ab
17	Placebo.ab
18	Drug therapy.fs
19	Randomly.ab
20	Trial.ab
21	Groups.ab
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	22 and 13
24	limit 23 to yr="2006 - 2012"
25	Review.pt and medline.tw
26	Meta-analysis.pt
27	Systematic$.tw and (review$ or overview$).tw
28	Meta?analy$.tw
29	Meta analy$.tw
30	25 or 26 or 27 or 28 or 29 or 30

31	30 and 13
32	limit 31 to yr="2006 - 2012"
33	Economics/
34	costs and cost analysis/
35	Cost allocation/
36	Cost-benefit analysis/
37	Cost control/
38	Cost savings/
39	Cost of illness/
40	Cost sharing/
41	deductibles and coinsurance/
42	Medical savings accounts/
43	Health care costs/
44	Direct service costs/
45	Drug costs/
46	Employer health costs/
47	Hospital costs/
48	Health expenditures/
49	Capital expenditures/
50	Value of life/
51	Exp economics, hospital/
52	Exp economics, medical/
53	Economics, nursing/
54	Economics, pharmaceutical/
55	Exp fees and charges/
56	Exp budgets/
57	(low adj cost).mp
58	(high adj cost).mp
59	(health?careadj cost$).mp
60	(fiscal or funding or financial or finance).tw
61	(cost adj estimate$).mp
62	(cost adj variable).mp
63	(unit adj cost$).mp
64	(economic$ or pharmacoeconomic$ or price$ or pricing).tw
65	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66	65 and 13
67	limit 66 to yr="2006 - 2012"
68	24 or 32 or 67

	ALL EBM Reviews
1	exp prostatic hyperplasia/
2	BPH.mp

3	BPO.mp
4	BPE.mp
5	(prostat* adj3 hyper*).tw
6	benign.tw AND (prostat* adj3 (enlarge* OR obstruct* OR disease)).tw
7	1 or 2 or 3 or 4 or 5 or 6
8	holmium laser.tw.
9	yag laser.tw.
10	(laser adj3 (enucleat* or prostatect* or resect* or ablat*)).tw.
11	holep.tw.
12	8 or 9 or 10 or 11
13	7 and 12
14	Randomized controlled trial.pt
15	Controlled clinical trial.pt
16	Randomized.ab
17	Placebo.ab
18	Drug therapy.fs
19	Randomly.ab
20	Trial.ab
21	Groups.ab
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	22 and 13
24	limit 23 to yr="2006 - 2012"
25	Review.pt and medline.tw
26	Meta-analysis.pt
27	Systematic$.tw and (review$ or overview$).tw
28	Meta?analy$.tw
29	Meta analy$.tw
30	25 or 26 or 27 or 28 or 29 or 30
31	30 and 13
32	limit 31 to yr="2006 - 2012"
33	Economics/
34	costs and cost analysis/
35	Cost allocation/
36	Cost-benefit analysis/
37	Cost control/
38	Cost savings/
39	Cost of illness/
40	Cost sharing/
41	deductibles and coinsurance/
42	Medical savings accounts/
43	Health care costs/
44	Direct service costs/
45	Drug costs/
46	Employer health costs/

47	Hospital costs/
48	Health expenditures/
49	Capital expenditures/
50	Value of life/
51	Exp economics, hospital/
52	Exp economics, medical/
53	Economics, nursing/
54	Economics, pharmaceutical/
55	Exp fees/
56	Exp charges/
57	55 and 56
58	Exp budgets/
59	(low adj cost).mp
60	(high adj cost).mp
61	(health?careadj cost$).mp
62	(fiscal or funding or financial or finance).tw
63	(cost adj estimate$).mp
64	(cost adj variable).mp
65	(unit adj cost$).mp
66	(economic$ or pharmacoeconomic$ or price$ or pricing).tw
67	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66
68	67 and 13
69	limit 66 to yr="2006 - 2012"
70	24 or 32 or 69

HTA agencies' websites searched

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness, Monash University	http://www.southernhealth.org.au/page/Health_Professionals/CCE/
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications/
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	http://www.ryerson.ca/library/info/databases/cabot.html
Centre for Health Economics and Policy Analysis (CHEPA),	http://www.chepa.org

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
McMaster University	
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://dsi.dk/
Finnish Office for Health Technology Assessment (FINOHTA)	http://finohta.stakes.fi/EN/index.htm
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
German Institute for Medical Documentation and Information (DIMDI)	http://www.dimdi.de/static/en/index.html

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
/ HTA	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.ac.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry [note: cannot locate this	http://www.tufts-nemc.org/cearegistry/index.html

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
[9MAR2010]	
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services	http://www.nlm.nih.gov/hsrph.html
Research and Health Care Technology (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Oregon Health Resources Commission (US)	http://www.nlm.nih.gov/hsrph.html
Office of Health Technology Assessment Archive (US)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/

Additional search terms – economic evaluations

Searches were performed on 13 November 2011.	Embase searches	Results
#economicspl-2 (#42)	#42.41 AND [2006-2012]/py	129
#economicspl-1 (#41)	#41.26 AND #41.40	229
#psectionandlsection-14 (#40)	#40.7 AND #40.13	880
#psectionandlsection-13 (#39)	#39.1 OR #39.2 OR #39.3 OR #39.4 OR #39.5	15,992
#psectionandlsection-12 (#38)	holep:ab,ti	232
#psectionandlsection-11 (#37)	(laser NEAR/3 (enucleat* OR prostatect* OR resect* OR ablat*)):ab,ti	6,466
#psectionandlsection-10 (#36)	'yag laser':ab,ti	9,571
#psectionandlsection-9 (#35)	'holmium laser':ab,ti	1,038
#psectionandlsection-8 (#34)	'holmium'/exp OR holmium AND laser:ab,ti	2,191
#psectionandlsection-7 (#33)	#33.1 OR #33.2 OR #33.3 OR #33.4 OR #33.5 OR #33.6	29,781
#psectionandlsection-6 (#32)	benign:ab,ti AND (prostat* NEXT/3 (enlarge* OR obstruct* OR disease)):ab,ti	1,729
#psectionandlsection-5 (#31)	(prostat* NEXT/3 hyper*):ab,ti	16,182
#psectionandlsection-4 (#30)	bpe:ab,ti	430
#psectionandlsection-3 (#29)	bpo:ab,ti	710
#psectionandlsection-2 (#28)	bph:ab,ti	9,411
#psectionandlsection-1 (#27)	'prostate hypertrophy'/exp OR 'prostate hypertrophy'	24,615

#healtheconomicsfilter-26 (#26)	#26.1 OR #26.2 OR #26.3 OR #26.4 OR #26.5 OR #26.6 OR #26.7 OR #26.8 OR #26.9 OR #26.10 OR #26.11 OR #26.12 OR #26.13 OR#26.14 OR #26.15 OR #26.16 OR #26.17 OR #26.18 OR #26.19 OR #26.20 OR #26.21 OR #26.22 OR #26.23 OR #26.24 OR #26.25	1,547,543
#healtheconomicsfilter-25 (#25)	managed NEXT/2 (care OR network?)	42,634
#healtheconomicsfilter-24 (#24)	(clinical OR critical OR patient) NEXT/1 (path? OR pathway?)	102,251
#healtheconomicsfilter-23 (#23)	decision NEXT/2 (tree$ OR analys$ OR model$)	9,339
#healtheconomicsfilter-22 (#22)	monte AND carlo	25,635
#healtheconomicsfilter-21 (#21)	markov$	12,873
#healtheconomicsfilter-20 (#20)	utilit$	61
#healtheconomicsfilter-19 (#19)	cua	1,299
#healtheconomicsfilter-18 (#18)	'cea'	32,332
#healtheconomicsfilter-17 (#17)	cba	14,755
#healtheconomicsfilter-16 (#16)	qaly$	4,388
#healtheconomicsfilter-15 (#15)	'quality adjusted life year$'	8,765
#healtheconomicsfilter-14 (#14)	hrqol$	6,788
#healtheconomicsfilter-13 (#13)	qol$	20,925
#healtheconomicsfilter-12 (#12)	'quality of life'/exp OR 'quality of life'	225,280
#healtheconomicsfilter-11 (#11)	'fee'/exp OR fee OR fees	39,645
#healtheconomicsfilter-10 (#10)	value NEXT/1 (money OR monetary)	4
#healtheconomicsfilter-9 (#9)	expenditure$	33,724
#healtheconomicsfilter-8 (#8)	budget$	25,636
#healtheconomicsfilter-7 (#7)	pharmacoeconomic? OR (pharmaco AND economic?)	167,274
#healtheconomicsfilter-6 (#6)	price? OR pricing?	9,155
#healtheconomicsfilter-5 (#5)	cost? OR costing? OR costly OR costed	197,715
#healtheconomicsfilter-4 (#4)	economic*	1,047,308
#healtheconomicsfilter-3	'quality of life'/exp OR 'quality of life'	225,280

(#3)		
#healtheconomicsfilter-2 (#2)	'health care cost'/exp OR 'health care cost'	168,320
#healtheconomicsfilter-1 (#1)	'health economics'/exp OR 'health economics'	523,416

Search results for the HTA database search at York CRD (encompasses DARE, NHS EED and HTA).

#1	(holep)
#2	(yag laser)
#3	(holmium laser)
#4	(holmium OR holmium AND laser)
#5	(prostat* NEXT/3 hyper*)
#6	(bpe)
#7	(bpo)
#8	(bph)
#9	(prostate hypertrophy)
#10	(benign AND (prostat* NEXT/3 (enlarge* OR obstruct* OR disease)))
#11	(laser NEXT/3 (enucleat* OR prostatect* OR resect* OR ablat*))
#12	#1 OR #2 OR #3 OR #4 OR #11
#13	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#14	#12 AND #13
Total results returned	**182**

Appendix A Studies included in the review

Systematic reviews included in the assessment report that were identified in the updated literature search HoLEP versus TURP

HTA and systematic reviews					
Author/Year	**Objective of report**	**Number & publication dates of included studies**	**Population considered in included studies** **Test comparison**	**Conclusions/ recommendation**	**Quality Assessment**
Author and year Lourenco et al (2008) **Country of origin** United Kingdom **HTA agency** NIHR HTA Programme **Updates** No.	**Aim/objectives of study** To determine the clinical effectiveness and cost utility of procedures alternative to TURP for benign prostatic enlargement (BPE) unresponsive to expectant, non-surgical treatments. Interventions considered: minimally invasive techniques (TUMT, TUNA, TEAP, transurethral laser coagulation) and tissue ablative procedures (laser prostatectomy, laser vaporisation, TUVP, TUVRP, bipolar TURP, bipolar TUVP and bipolar TUVRP). **Study design** Systematic literature reviews and meta-analysis were carried out. Markov modelling and cost-utility analysis were conducted.	**Databases searched** 13 databases, incl. MEDLINE, EMBASE, MEDLINE In-Process, BIOSIS, ISI Science Citation Index, ISI Proceedings, Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, HTA Database, National Research Register, Clinical Trials, Current Controlled Trials. Also conference proceedings of: European Assoc. Of Urology, the American Urological Assoc., British Assoc. Of Urological Surgeons **Time period of search** 1966-2006 **Number of studies included**	**Population:** Trials of men with a clinical diagnosis of BPE who have undergone surgery were included. Patients undergoing conservative management (watchful waiting or medical therapy) were excluded. **NB: intervention and comparator are inverted in the report:** **Report:** Intervention: TURP Comparator: HoLEP **Evaluation for MSAC:** Intervention: HoLEP Comparator: TURP	**Overall study conclusion:** In the absence of strong evidence in favour of newer methods, TURP remains both clinically effective and cost-effective. There is a need for further research to establish (i) how many years of medical treatment are necessary to offset the cost of treatment with a minimally invasive or ablative intervention; (ii) more cost-effective alternatives to TURP; (iii) strategies to improve outcomes after TURP. **Conclusions specific to HoLEP/TURP:** In terms of effectiveness, HoLEP would appear to be unique amongst the newer technologies in offering an advantage over TURP, although, based on the current short-term outcome data available, this is confined to the urodynamic outcome, which may not be of importance to patients. Longer-term outcome data are awaited.	**Quality: High** Explicit review questions[4]: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: Yes Heterogeneity between studies assessed: Yes Summary of main results clear and appropriate: Yes

[4] Has no PICO or actual explicit review questions, but does provide *very clear* inclusion criteria (page 23)

		by indication Entire report: 158 reports, describing 88 RCTs[3] HoLEP and TURP comparison: 15 papers, describing 5 RCTs.			

Results

All results reported using a fixed effects model, unless otherwise stated.

Safety:

(a) Immediate complications: HoLEP had lower rate of *blood transfusion* than TURP (5 studies, 1/293 HoLEP vs. 9/287 TURP, RR 0.27, 95% CI 0.07-0.94, p=0.04). The occurrence of *urinary retention* for HoLEP and TURP was similar, but with wide confidence intervals (5 studies, 15/293 HoLEP vs. 21/287 TURP, RR 0.71, 95% CI 0.38-1.32, p=0.28). The occurrence of *urinary tract infection* for HoLEP and TURP was similar, but with wide confidence intervals (2 studies, 5/91 HoLEP vs. 5/89 TURP, RR 0.98, 95% CI 0.31-3.09, p=0.97). *TUR syndrome* was reported in only 1 study with 1 event reported in the TURP arm (1 study, 0/52 HoLEP vs. 1/48 TURP, RR 0.31, 95% CI 0.01-7.39, p=0.47). *Mortality rates*: 2 studies, 1/91 HoLEP vs. 2/89 TURP, RR 0.59, 95% CI 0.08 to 4.39, p=0.61. *Capsular perforation rates*: 1 study, HoLEP n=1 (2.0%), TURP n=0 (0.0%), p=NR.

(b) Longer-term complications: *Stricture* for HoLEP and TURP was similar but with wide confidence intervals (5 studies, 15/287 HoLEP vs. 17/273 TURP, RR 0.84, 95% CI 0.43-1.65, p=0.61). *Urinary incontinence* for HoLEP and TURP was similar but with wide confidence intervals (4 studies, 55/252 HoLEP vs. 54/253 TURP, RR 0.97, 95% CI 0.72-1.31, p=0.83). The *erectile dysfunction* rates were higher for HoLEP (n=2, 9.09%) than for TURP (n=2, 7.69%) but statistically insignificant (p=0.86) (reported on the basis of 1 study).

Effectiveness:

(a) Symptoms: *symptom scores* were better for HoLEP than TURP. Scores at 6 months: 5 studies, WMD -0.91, 95% CI -1.05 to -0.77, p=0.00001. Scores at 12 months (using the fixed effects model): 5 studies, WMD -0.42, 95% CI -0.52 to -0.32, p=00001. (Because heterogeneity was high, random effects model was applied; WMD still favoured HoLEP, but the difference was no longer statistically relevant: WMD -0.80, 95% CI -1.70 to 0.10, p=0.08). Scores at 4 years: 1 study, WMD -1.40, 95% CI -3.91 to 1.11, p=0.27. The data also indicate that *peak urine flow rate* was better after HoLEP than after TURP at 3 and 12 months after the interventions (NB: although these results are statistically significant, the difference is small and therefore may not be clinically relevant). At 3 months: 2 studies, WMD 3.49 ml/s, 95% CI 0.63-6.35, p=0.02. At 6 months: 5 studies, WMD -4.05, 95% CI -4.51 to 3.60, p<0.00001. At 12 months: 5 studies, WMD 1.43, 95% CI 0.92 to 1.93, p<0.00001. At 24 months: 2 studies, WMD 3.16, 95% CI -0.49 to 6.81, p=0.09. *Post void residual volume*: at 6 months: 2 studies, WMD -12.02, 95% CI -16.31 to -7.74, p<0.00001; at 12 months: 1 study, WMD -21.30, 95% CI -34.46 to -8.14, p=0.002. *Prostate volume*: at 6 months: 1 study, WMD -18.20, 95% CI -27.52 to -8.88, p=0.0001.

(b) Quality of Life: was assessed using IPSS QoL questionnaire; quality of life does not appear to differ between HoLEP and TURP. At 6 months: 3 studies, WMD 0.25, 95% CI 0.05 to 0.44, p=0.01. At 12 months: 3 studies, WMD 0.06, 95% CI -0.26 to 0.38, p=0.73, with marked heterogeneity.

[3] The '158 reports' is taken from chapter 5 (page 25). The abstract (page iii) erroneously states that 156 reports were examined.

(c) Re-operation: the occurrence of re-operation for HoLEP and TURP was similar but with wide confidence intervals (4 studies, 10/231 HoLEP vs. 15/232 TURP, RR 0.68, 95% CI 0.32-1.44, p=0.31).

Cost-effectiveness:

(a) The duration of operation was on average 17 minutes longer for HoLEP than for TURP (5 studies, WMD 16.96, 95% CI 13.45 to 20.47, p<0.00001).

(b) The hospital stay length was significantly shorter for HoLEP than for TURP (4 studies, WMD -1.05, 95% CI -1.20 to -0.89, p<0.00001).

HoLEP as a single treatment was found to be cost-effective for a willingness to pay up to about £4556 per QALY.

Studies included in the assessment report that were identified in the updated literature search HoLEP versus TURP

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
Ahyai et al 2007 **NB: This is a follow-up to the Kuntz et al 2004 study (which is included in Lourenco et al 2008)** Urology Dept, Auguste-Viktoria-Hospital, Berlin, Germany Single centre Operations performed: June 1999–December 2001 n=200 (100 patients in HoLEP group, 100 patients in TURP group)	**Objective** To report 3-year follow-up results of a randomised controlled trial comparing holmium laser enucleation of the prostate (HoLEP) with transurethral resection of the prostate (TURP). **Study design** Randomised controlled trial **Follow-up** 3 years (drop-out at 3 years: 56/200 patients – 25/100 in HoLEP group; 31/100 in TURP group) **Intervention**: HoLEP + mushroom technique **Comparator**: TURP	**Inclusion/exclusion criteria** *Inclusion* - AUA score ≥12 - Q max ≤12 ml/s - PVR volume ≥50 ml - Schafer grade ≥2 in pressure flow studies - Total prostate volume <100 cc in transrectal ultrasound *Exclusion* - Previous prostate or urethral surgery - Voiding disorders not related to BPH **Patient characteristics** *Age (years): mean (range)*	**OUTCOMES** **Effectiveness** - Peak flow (ml/s; mean ± SD) At 1 month: HoLEP: 23.1±7.1; TURP 25.5±10.7; p=0.20 At 6 months: HoLEP: 25.1±6.9; TURP 25.1±9.4; p=0.72 At 12 months: HoLEP 27.9±9.9; TURP 27.7±12.2; p=0.76 At 2 years: HoLEP 28.0±9.0; TURP 29.1±10.9; p=0.82 At 3 years: HoLEP 29.0±11.0; TURP 27.5±9.9; p=0.41 - AUA symptom score (mean ± SD)	**Level II evidence** ***Original study quality assessed as part of Lourenco 2008***

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
		HoLEP: 68.0 (56–88) TURP: 68.7 (52–86) *AUA symptom score: mean (range)* HoLEP: 22.1 (13–33) TURP: 21.4 (12–32) *Q max (ml/s): mean (range)* HoLEP: 4.9 (0–11) TURP: 5.9 (0–12) *Prostate vol. (ml): mean (range)* HoLEP: 53.5 (20–95) TURP: 49.9 (20–99) *PVR volume (ml): mean (range)* HoLEP: 238 (50–1000) TURP: 216 (50–800)	At 1 month: HoLEP 4.3±2.9; TURP 5.5±3.8; p=0.04 At 6 months; HoLEP 2.2±1.6; TURP 3.7±3.4; P=0.006 At 12 months: HoLEP 1.7±1.8; TURP 3.9±3.9; p<0.0001 At 2 years: HoLEP 1.7±1.7; TURP 3.9±3.7 p<0.0001 At 3 years: HoLEP 2.7±3.2; TURP 3.3±3.0; p=0.17 - Post-void residual volume (ml; mean ± SD) At 1 month: HoLEP 9.4±19.3; TURP 13.2±19.4; p=0.03 At 6 months: HoLEP 4.8±12.5; TURP 16.7±16.9; p<0.0001 At 12 months: HoLEP 5.3±15.3; TURP 26.6±60.4; p<0.0001 At 2 years: HoLEP 5.6±19.9; TURP 19.9±29.6; p<0.0001 At 3 years: HoLEP 8.4±16.0; TURP 20.2±33.0; p<0.012 Adverse events (from lost to follow-up of excluded patients): 3 years: BPH recurrence: HoLEP 1; TURP 0 Bladder neck contracture: HoLEP 0; TURP 1 Urethral stricture: HoLEP 1; TURP 2 Death: HoLEP 0; TURP 1	
Gilling et al 2011 NB: 7-year follow-up to Tan et al 2003	**Objective** To assess the durability of holmium laser enucleation of prostate in comparison to transurethral	**Inclusion/exclusion criteria** *Inclusion* - Prostate volume of 40–200 ml (as calculated by TRUS volume)	**OUTCOMES** **Effectiveness**	**Level II evidence** ***Original study quality assessed as part of Lourenco 2008***

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
New Zealand Single centre Patients were enrolled between June 1997 and December 2000 N=61 (31 in HoLEP group, 30 in TURP group), randomised	resection of the prostate (TURP). **Study design** Randomised controlled trial **Follow-up** 92 months; (30 patients lost to follow-up; 14 HoLEP and 17 TURP patients remaining) **Intervention:** HoLEP with tissue morcellation **Comparator:** TURP	- Qmax ≤15 ml/s - AUA symptom score ≥8 - Post-void residual volume <400 ml - Schafer grade ≥2 *Exclusion* - Previous prostatic or urethral surgery - Carcinoma of the prostate - In urinary retention**Patient characteristics** Age (years): mean ± SD: HoLEP: 71.70±1.10 TURP: 70.30± 1.00 **AUA score: mean ± SD:** HoLEP: 26.39±6.14 TURP: 23.72±6.44 **Qmax (ml/s): mean ± SD** HoLEP: 8.28±2.18 TURP: 8.26±2.18 Prostate volume (ml): mean ± SD: HoLEP: 77.68±32.13 TURP: 70.00±27.78 PVR volume (ml): mean ± SD: HoLEP: 116.14±85.09 TURP: 126.67±116.77	- Peak flow (ml/s; mean ± SD) At 1 month: HoLEP: 22.3±2.3; TURP: 18.4±1.6; p=NR At 92 months: HoLEP 22.09±15.47; TURP 17.83±8.61; p=NR - AUA symptom score (mean ± SD) At 1 month: HoLEP 8.6±1.2; TURP 5.7±1.1; p=NR At 92 months: HoLEP 8.0±5.20; TURP 10.3±7.42; p=NR - Quality of life (mean ± SD) At 92 months: HoLEP 1.47±1.30; TURP 1.31±0.85; p=NR - Treatment failure/re-treatment rate (n; at 92 months): HoLEP nil; TURP 3; p=NR	
Eltabey et al 2010	**Objective**	**Inclusion/exclusion criteria**	**OUTCOMES**	**Level II evidence**

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
Saudi Arabia Single centre Recruitment period: April 2008–December 2009 N=80	To compare the safety, efficacy and medium-term durability of holmium laser enucleation of the prostate (HoLEP) combined with mechanical morcellation versus standard transurethral resection of the prostate (TURP). **Study design** Randomised controlled trial **Follow-up** At 1, 6, and 12 months; complete for 100% of randomised patients **Intervention:** HoLEP **Comparator:** TURP	*Inclusion* - Patients who presented with BOO (bladder outlet obstruction) caused by BPH - Related voiding symptoms - Prostate volume greater than 30 g but less than 100 g (as determined by TRUS) - Had not responded to pharmacologic therapy - Eligible for surgical treatment - AUA symptom score ≥12 - Qmax ≤15 ml/s *Exclusion* - Neurogenic bladder - Previous urethral, bladder neck or prostate surgery - Suspected prostatic cancer by abnormal digital rectal examination (DRE), total serum PSA >4 ng/ml or abnormal TRUS - **TRUS-guided prostate biopsy** Patient characteristics Age – mean ± SD: HoLEP: 67.5 ± 8.1 years TURP: 68.3 ± 9.2 years Prostate volume (g) – mean ± SD: HoLEP: 62.4 ± 24.1 g TURP: 58.5 ± 31.6 g Qmax (ml/s) – mean ± SD	**Safety** **Immediate complications** **-** Blood transfusion (number; (%): HoLEP 0 (0%); TURP 3 (7.5%); p<0.007 Longer term complications - Urethral stricture (number (%)); at 12 months: HoLEP 1 (2.5%); TURP 2 (5%); p=0.72 - Urinary incontinence (number, %); at 6 months: HoLEP 8(20%); TURP 12 (30%); p=0.08 This includes Urinary urge incontinence HoLEP 3 (7.5%); TURP 5 (12.5%); p=NR Stress incontinence HoLEP2 (5%); TURP 3 (7.5%); p=NR Mixed incontinence HoLEP1 (2.5%); TURP 2 (5%); p=NR **Effectiveness** **-** Peak flow (ml/s; mean ± SD): At 1 month: HoLEP 22.3 ± 12.2; TURP 23.1 ± 10.6; p=0.64; At 6 months: HoLEP 23.5±9.2; TURP 24.3±6.8; p=0.72; At 12 months: HoLEP 24.9±11.7; TURP 25.5±7.4; p=0.78 - AUA symptom score (mean ± SD): At 1 month: HoLEP 4.1±2.7; TURP 5.3±3.4; p=0.05; At 6 months: HoLEP 2.6±1.3; TURP 3.8±3.1;p=0.005; At 12 months: HoLEP 2.2±1.4; TURP 3.7±1.6; p<0.0001 - Post-void residual volume (ml; mean ± SD) At 1 month: HoLEP 9.6±20.1; TURP 15.3±22.4; p=0.005	**Risk of bias/study quality** Random sequence generation unclear risk No details given the authors simply state that this is a prospective randomised study Allocation concealment: unclear risk No details given the authors simply state that this is a prospective randomised study Blinding: unclear risk Difficult to achieve with a surgery trial - while most measures were objective IPSS was assessed. Incomplete outcome data: low risk Lost to follow-up was not explicitly reported - longest follow-up was 12 months. Assumed that no patients were lost to follow-up Other bias: unclear Single centre study

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
		HoLEP: 8.4 ± 2.3 ml/s TURP: 8.1± 2.7 ml/s PVR urine volume (ml) – mean ± SD HoLEP: 130 ± 96.5 ml TURP: 105 ± 89.7 ml AUA symptom score – mean ± SD HoLEP: 23 ± 3.6 TURP: 25 ± 5.1	At 6 months: HoLEP 5.7±12.6; TURP 17.6±18.3; p< 0.0001 At 12 months: HoLEP 5.3±15.2; TURP 24.1±16.8; p<0.0001 - Prostate volume (g; mean ± SD): HoLEP 44.2±16.5; TURP 37.4±19.2; p=0.08 **Cost** - Length of operation (minutes; mean ± SD): HoLEP 72.8±21.7; TURP 73.6±22.3; p=0.15 - Length of catheterisation (days; mean ± SD): HoLEP 1.5±1.4; TURP 2.1±1.1; p<0.0001 - Length of hospital stay (days; mean ± SSD): HoLEP 2.6±1.2; TURP 3.8±1.6; p< 0.0001	
Mavuduru et al 2009 India Single centre Recruitment period not reported N=30, randomised (n=27 at 9 months)	**Objective** To compare the safety and efficacy of transurethral resection of the prostate (TURP) and holmium laser prostatectomy. **Study design** Randomised controlled trial **Follow-up** 9 months (3 patients lost to follow-up at 9 months) **Intervention:** HoLEP (NB: morcellation was only used in one patient) **Comparator:** TURP	**Inclusion/exclusion criteria** *Inclusion* - Patients eligible for surgery for symptomatic BPH *Exclusion* - Patients with a history of previous prostatic or urethral surgery - Documented cases of prostate carcinoma - Patient characteristics Age (years): mean ± SD: HoLEP: 69.86 ± 9.6 TURP: 66.46 ± 5.79 IPSS symptom score: mean ± SD: HoLEP: 22.53 ± 4.79 TURP: 21.4 ± 3.7 Qmax (ml/s): mean ± SD	**OUTCOMES** **Safety** Immediate complications - Blood transfusion (number, (%): HoLEP nil; TURP 1/15 (6.66%); p=NR - Capsular perforations (number, (%): HoLEP 1/15 (6.66%); TURP nil; p=NR Longer term complications - Urethral stricture (number) At 3 week: HoLEP 0/15; TURP 2/15 p=NS At 3 months: HoLEP 0/15; TURP 1/15; p=NS At 9 months: HoLEP 0/14; TURP 0/13; p=NS - Urinary incontinence (number): At 3 weeks HoLEP 0/15; TURP 1/15 p=NS At 3 months: HoLEP 1/15; TURP 0/15; p=NS At 9 months: HoLEP 1/14; TURP 0/13; p=NS Complications of adverse events after catheter removal Transient dysuria HoLEP 1/15; TURP 3/15; p=NS	**Level II evidence** **Risk of bias/study quality** Random sequence generation: low risk Randomised using a computer-generated random number table Allocation concealment: unclear risk No details given the authors simply state that this is a randomised study Blinding: unclear risk. Difficult to achieve with a surgery trial – while most measures were objective IPSS was assessed. Incomplete outcome data: low risk3 patients were lost to follow-up no further details are given (2 in HoLEP group; 1 in TURP group) Other bias: unclear

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
		HoLEP: 5.79 ± 2.7 TURP: 6.9 ± 2.5 Prostate volume (g): mean ± SD: HoLEP: 36.53 ± 12.33 TURP: 36.33 ± 11.4 PVR volume (ml): mean ± SD HoLEP: 91 ± 30 TURP: 103 ± 27	Recatheterisation HoLEP 1/15; TURP 1/15; p=NS Bleeding HoLEP 0/15; TURP 2/15; p=NS Incontinence HoLEP 2/15; TURP 0/15; p=NS **Effectiveness** - Symptom score (IPSS) At 3 months: HoLEP 2.26±1.57; TURP 2.86±1.72; p=0.329 At 9 months: HoLEP 4.23±1.25; TURP 3.57±1.03; p=0.37 - Post-void residual volume (ml; mean ± SD) At 3 months: HoLEP 13±8.61; TURP 13.66±14.0; p=0.87 At 9 months: HoLEP 43±10.61; TURP 35.66±15.0; p=0.97 - Prostate volume (g; mean ± SD): HoLEP 6.53±0.52; TURP 20±1.66; p<0.001 Cost - Length of operation (minutes; mean ± SD): HoLEP 53±9.84; TURP 43±9.36; p<0.01 - Length of catheterisation (hours; mean ± SD): HoLEP 46.42±14.25; TURP 78.20±17.84; p<0.001	Single centre study

Studies included in the assessment report that were identified in the updated literature search HoLEP versus OP

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
Naspro et al 2006 Italy Single centre Recruitment period: March 2003–December 2004 N = 80, randomised (41 in HoLEP group, 39 in OP group)	**Objective** To prospectively evaluate perioperative outcomes and 2-year follow-up after holmium laser enucleation (HoLEP) and standard open prostatectomy (OP) for treating benign prostatic hyperplasia-related obstructed voiding symptoms, with prostates >70 g. **Study design** Randomised controlled trial **Follow-up** 24 months (follow-up – 65 patients; 35 in HoLEP group, 30 in OP group) **Intervention**: HoLEP with tissue morcellation **Comparator**: OP	**Inclusion/exclusion criteria** *Inclusion* - BPH-related obstructed voiding symptoms - Prostate volume >70 g (as determined by transrectal ultrasound) - Non-response to pharmacologic therapy - Post-voiding residue <150 ml - Peak urinary flow rate <15 ml/s - Urodynamic obstruction (Shafer grade >2) *Exclusion* - Neurogenic bladder - History of adenocarcinoma of the prostate - Previous prostatic, bladder-neck or urethral surgery **Patient characteristics** *Age (years): mean ± SD:* HoLEP: 66.26 ± 6.55 OP: 67.27 ± 6.72 *IPSS symptom score: mean ± SD:* HoLEP: 20.11 ± 5.84 OP: 21.60 ± 3.24 *Q max (ml/s): mean ± SD*	**OUTCOMES** **Safety** - Homologous blood transfusion (n, (%): HoLEP nil; OP 2 (5.1%); p<0.007 - Autologous blood transfusion (n, (%): HoLEP 2 (4%); OP 5 (12.8%); p<0.001 - Acute urinary retention – 0-3 months post-op (n, (%): HoLEP 5 (12.1%); OP 2 (5.1%); p=0.11 - Urethral stricture (n, %) At 12 months: HoLEP 2 (5.4%); OP 2 (5.7%); p=0.3 At 24 months: HoLEP 1 (2.8%); OP 1 (3.3%); p=0.3 Other complications: 3 months Bladder mucosal injury HoLEP 3/41; TURP 0/39 Transitory urge incontinence HoLEP 14/41; TURP 17/39 Dysuria: HoLEP 28/41; TURP 16/39 Stress incontinence: HoLEP 1/41; TURP 1/39 Reintervention for bleeding HoLEP 1/41; TURP 1/39 12 months Urge incontinence HoLEP 2/41; TURP 3/39 Dysuria: HoLEP 4/41; TURP 3/39 24 onths Dysuria: HoLEP 1/35; TURP 1/30 ***Effectiveness***	**Level II evidence** **Risk of bias/study quality** Random sequence generation low risk Randomised using a computer generated random number table Allocation concealment: unclear risk No details given; the authors simply state that this is a prospective randomised study Blinding: unclear risk Difficult to achieve with a surgery trial – while most measures were objective IPSS was assessed. Incomplete outcome data: unclear risk At 24 months 15 patients were lost to follow-up; no further details are given (5 in HoLEP group; 10 in OP group) Other bias: unclear Single centre study

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
		HoLEP: 7.83 ± 3.42 OP: 8.32 ± 2.37 *Prostate volume (g): mean ± SD:* HoLEP: 113.27 ± 35.33 OP: 124.21 ± 38.52	- Peak flow 12 months: HoLEP 22.32±3.8; OP 24.21±6.49; p=0.27 24 months: HoLEP 19.19±6.3; OP 20.11±8.8; p=0.91 - IPSS Symptom score 12 months: HoLEP 8.45±5.87; OP 8.40±6.0; p=0.98 24 months: HoLEP 7.9±6.2; OP 8.1±7.1; p=0.44 - Quality of Life 12 months: HoLEP 1.7±0.94; OP 1.77±0.83; p=0.85 24 months: HoLEP 1.5±0.87; OP 1.66±0.76; p=0.76 ***Cost*** - Length of operation (min; mean ± SD): HoLEP 72.09±21.22; OP 58.31±11.95; p<0.0001 - Length of catheterisation (d; mean ± SD): HoLEP 1.5±1.07; 4.1±0.5; p<0.0001 - Length of hospital stay (days; mean ± SD): HoLEP 2.7±1.1; OP 5.43±1.05; p<0.0001	
Kuntz et al 2008 Kuntz et al 2004 Dept. of Urology, Auguste-Viktoria-Hospital, Berlin, Germany Single centre Recruitment period: not	**Objective** To report results of a randomised clinical trial comparing holmium laser enucleation of the prostate (HoLEP) with open prostatectomy (OP). Study design Randomised Controlled Trial Follow-up	Inclusion/exclusion criteria Inclusion - AUA score ≥ 8 - Qmax ≤ 12ml - PVR volume ≥ 50ml - Schafer grade ≥ 2 in pressure flow studies - Total prostate volume ≥ 100cm in transrectal ultrasound Exclusion	**OUTCOMES** **Safety** **-** Blood transfusion (n, (%): HoLEP nil; OP 8 (13.3%); p=0.003 1 month: Bladder Neck Contracture (BNC) HoLEP 0/60; OP 1/60 3 months:	**Level II evidence** **Risk of bias/study quality** Random sequence generation low risk. Patients were randomised with a scheduled balanced in blocks of 4 Allocation concealment: unclear risk/not described Blinding: unclear risk. Difficult to

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
reported N=120 (60 in OP group, 60 in HoLEP group)	5 years; 46 patients lost to follow-up at 5 years (18 lost in HoLEP, 28 lost in OP group) Intervention: HoLEP with mushroom technique (first 50 HoLEP patients) or morcellation (last 10 HoLEP patients) Comparator: OP	- Previous prostate or urethral surgery - Non-BPH voiding disorders Patient characteristics Age (years): mean ± SD: HoLEP: 69.2±8.4 OP: 71.2± 8.3 AUA symptom score: mean ± SD: HoLEP: 22.1±3.3 OP: 21.0± 3.6 Qmax (ml/s): mean ± SD HoLEP: 3.8±3.6 OP: 3.6± 3.8 Prostate volume (ml): mean ± SD: HoLEP: 114.6±21.6 OP: 113.0±19.2 PVR volume (ml): mean ± SD HoLEP: 280±273 OP: 292± 191	BNC HoLEP 0/57; OP 1/53 Urethral stricture HoLEP 1/60; OP 0/60 Death HoLEP 0/60; OP 2/60 18 months Urethral stricture HoLEP 1/56; OP 0/49 Death HoLEP 1/56; OP 0/49 24 months BNC HoLEP 0/53; OP 1/49 Urethral stricture HoLEP 0/53; OP 1/49 48 months BNC HoLEP 1/48; OP 0/40 Death HoLEP 0/48; OP 2/40 60 months Death HoLEP 1/45; OP 3/36 Continence: Transitory: HoLEP 2/60; OP 5/60 complained of urge incontinence which resolved by 1 month In 11 patients HoLEP 5/60; OP 6/60 who had been continent preoperatively some moderate to severe incontinence developed – resolving in all but one HoLEP patient by 3 months **Effectiveness** **-** Peak flow (ml/s, mean ± SD) At 3 months: HoLEP 27.6±7.0; OP 27.3±6.2; p<0.0001 At 6 months: HoLEP 29.9±8.8; OP 27.0±0.5; p<0.0001 At 1 year: HoLEP 27.4±9.7; OP 28.3±7.5; p=0.86 At 3 years: HoLEP 27.0±9.8; OP 25.3±6.9; p=0.32	achieve with a surgery trial – while most measures were objective IPSS was assessed. Incomplete outcome data: low risk. Five years postoperatively 38.3% of patients lost to follow-up; reasons are given although it is not stated whether any differences between the two groups Other bias: unclear Single centre study

Author & year Setting N	Study objective & design	Study population	Results	Study quality and applicability
			At 5 years: HoLEP 24.3±10.1; OP 24.4±7.4; p=0.97 - AUA symptom score (mean ± SD) At 3 months: HoLEP 3.3±2.7; OP 3.6±2.7; p<0.0001 At 6 months: HoLEP 2.4±1.9; OP 2.8±3.9; p<0.0001 At 1 year: HoLEP 2.3±2.0; OP 2.3±1.7; p=0.94 At 3 years: HoLEP 3.0±3.1; OP 2.8±1.6; p=0.82 At 5 years: HoLEP 3.0±3.2; OP 3.0±1.7; p=0.98 - Post-void residual volume (ml; mean ± SD) At 3 months: HoLEP 7.2±18.8; OP 3.0±7.7; p<0.0001 At 6 months: HoLEP 4.4±11.0; OP 2.1±6.0; p<0.0001 At 1 year: HoLEP 5.8±16.7; OP 6.4±12.3; p=0.83 At 3 years: HoLEP 6.1±12.1; OP 4.4±10.5; p=0.50 At 5 years: HoLEP 10.6±24.4; OP 5.3±11.2; p=0.25 - Re-treatment rate at 18 months (n): HoLEP 5; OP 3; p=NR Cost - Length of operation (minutes; mean ± SD): HoLEP 135.9±31.2; OP 90.6±19.5; p<0.0001 - Length of catheterisation (hours; mean ± SD): HoLEP 30.8±17.3; OP 194.4±20.1; p<0.0001 - Length of hospital stay (hrs; mean ± SD): HoLEP 69.6±36.4; OP 251.0±45.5; p<0.0001	

Appendix D Existing Systematic Reviews and HTA reports

The list of electronic databases and websites of agencies involved in HTA are provided in Appendix C. Our searches yielded 9 systematic reviews: Lourenco et al 2008, (Australia and New Zealand Horizon Scanning Network (ANZHSN) 2010), (Obyn & Mambourg 2008), (Medical Advisory Secretariat 2006), Ahyai et al 2010, Biester et al 2011, Herrmann et al 2009, Rieken et al 2010 and (Tan et al 2007).

The reports were assessed for quality; quality was found to vary from low to high. Three reports were of high quality, three reports were of fair quality and three reports were of low quality. Four reports compared HoLEP with TURP and the five remaining reports compared HoLEP with TURP and OP. None of the reports compared HoLEP with OP alone.

Author Year Country	Methods	Quality assessment
Lourenco et al 2008 UK	Databases searched: 13 databases, incl. MEDLINE, EMBASE, MEDLINE In-Process, BIOSIS, ISI Science Citation Index, ISI Proceedings, Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, HTA Database, National Research Register, Clinical Trials, Current Controlled Trials. Also conference proceedings of: European Assoc. Of Urology, the American Urological Assoc., British Assoc. Of Urological Surgeons Time period of search: 1966–2006 Comparators: HoLEP vs TURP Outcomes: Safety, effectiveness, cost-effectiveness	Quality: High Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: Yes Heterogeneity between studies assessed: Yes Summary of main results clear and appropriate: Yes (NB: Has no PICO or actual explicit review questions, but does provide *very clear* inclusion criteria (page 23))
ANZHSN 2010 Australia	Databases searched: AustHealth, Australian Medical index, CINAHL, Cochrane Library, Current Contents, Embase, Pre-Medline, Medline, PyscINFO, RACS electronic library. 11 HTA websites were also searched. Time period of search: To 20 March 2010 Comparators: HoLEP versus TURP and OP Outcomes: Safety, effectiveness, cost-effectiveness	Quality: Low Explicit review questions: No Explicit & appropriate eligibility criteria: No Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: No. Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: Yes
Obyn & Mambourg (KCE) 2008 Belgium	Databases searched: Medline and the Cochrane Database of Systematic Reviews. Also, HTA agencies' websites were searched for relevant HTA reports. Time period of search: 2002–2008 Comparators: HoLEP versus TURP Outcomes: Only one HoLEP-relevant study assessed in this report.	Quality: High Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: Yes Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: Yes
Medical Advisory Secretariat (MAS) 2006 Canada	Databases searched: OVID Medline, Medline In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library, INAHTA. Time period of search: 1 January 2000– 21 June 2006 Comparators: HoLEP versus TURP and OP Outcomes: Safety, effectiveness, cost-effectiveness	Quality: Fair Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: No Methods of study appraisal reproducible: No. Heterogeneity between studies assessed: Yes Summary of main results clear and appropriate: Yes (NB: PICO not provided, but research question clearly stated (page 23))
Ahayi et al 2010 Multinational	Databases searched: Medline. Time period of search: 1997 to 2009 Comparators: HoLEP versus TURP	Quality: Low Explicit review questions: No Explicit & appropriate eligibility criteria: No Explicit & comprehensive search strategy: No Quality of included studies appraised: No

	Outcomes: Safety, effectiveness, cost-effectiveness	Methods of study appraisal reproducible: No. Heterogeneity between studies assessed: No Summary of main results clear and appropriate: Yes (NB: Heterogeneity was assessed (page 385) but not reported.)
Biester et al 2011 Germany	Databases searched: Medline, Embase, the Cochrane Central Register of Controlled Trials (Clinical Trials), Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews) and the Health Technology Assessment Database (Technology Assessments). Time period of search: Up to October 2009 Comparators: HoLEP versus TURP and OP Outcomes: Effectiveness	Quality: High Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: Yes Methods of study appraisal reproducible: Yes Heterogeneity between studies assessed: Yes Summary of main results clear and appropriate: Yes
Hermann et al 2009 Multinational	Databases searched: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), HTA Database, the Prostatic Diseases and Urologic Cancers Group registry, Science Citation Index, reference lists of all identified trials and previous reviews. Time period of search: January 1995–December 2008 Comparators: HoLEP versus TURP and OP Outcomes: Effectiveness	Quality: Fair Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: Yes Quality of included studies appraised: No Methods of study appraisal reproducible: No. Heterogeneity between studies assessed: N/A Summary of main results clear and appropriate: Yes
Rieken et al 2010 Switzerland	Databases searched: Medline. Time period of search: Approx. 2005-2009 (the article indicates that data were based on a MEDLINE search conducted "over the past 4 years"; the article was received for publication on July 28, 2009.) Comparators: HoLEP vs. TURP and OP. Outcomes: safety, effectiveness.	Quality: Low Explicit review questions: No Explicit & appropriate eligibility criteria: No Explicit & comprehensive search strategy: No Quality of included studies appraised: No Methods of study appraisal reproducible: No. Heterogeneity between studies assessed: N/A. Summary of main results clear and appropriate: Yes (NB: Levels of evidence were assessed, however, the quality of evidence was NOT assessed.)
Tan et al 2007 China	Databases searched: Medline, Embase and The Cochrane Library. Time period of search: 1990–2007. Comparators: HoLEP versus TURP Outcomes: Safety, effectiveness, cost-effectiveness	Quality: Fair Explicit review questions: Yes Explicit & appropriate eligibility criteria: Yes Explicit & comprehensive search strategy: No Quality of included studies appraised: Yes Methods of study appraisal reproducible: Yes. Heterogeneity between studies assessed: Yes Summary of main results clear and appropriate: No (NB: Has no PICO or actual explicit review questions, but does provide very clear inclusion criteria (page 1202))

Appendix E Excluded studies

Wrong publication type

1. Aho, TF & Gilling, PJ, 2008. 'Current techniques for laser prostatectomy-PVP and HoLEP', *Archivosespanoles de urologia,* 61, 1005-1013.

2. Centre for Reviews and Dissemination, 2006. 'A clinical outcomes and cost analysis comparing photoselective vaporization of the prostate to alternative minimally invasive therapies and transurethral prostate resection for the treatment of benign prostatic hyperplasia (Structured abstract)'[internet]. NHS Economic Evaluation Database (NHSEED). Available from: http://www.ncbi.nlm.nih.gov/pubmed/16952668 [accessed 26 April 2012].

3. Centre for Reviews and Dissemination, 2003. 'A systematic review of holmium laser prostatectomy (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12003008492&UserID=0 [accessed 30 April 2012].

4. Centre for Reviews and Dissemination, 2000. 'A systematic review of the clinical efficacy and effectiveness of the holmium: YAG laser in urology (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=11999004093&UserID=0 [accessed 30 April 2012].

5. Centre for Reviews and Dissemination, 2008. 'Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomised controlled trials (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12008103393&UserID=0 [accessed 30 April 2012].

6. Centre for Reviews and Dissemination, 2009. 'Efficacy and safety of holmium laser prostatectomy: a systematic review (Provisional abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12005000394&UserID=0 [accessed 30 April 2012].

7. Centre for Reviews and Dissemination, 2004. 'Laser prostatectomy versus transurethral resection for treating benign prostatic obstruction: a systematic review (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12003000176&UserID=0 [accessed 30 April 2012].

8. Centre for Reviews and Dissemination, 2011. 'Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from:

http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12010006327&UserID=0 [accessed 30 April 2012].

9. Centre for Reviews and Dissemination, 2009. 'Surgical treatments for men with benign prostatic enlargement: cost-effectiveness study (Structured abstract)'. NHS Economic Evaluation Database (NHSEED) [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=22009101385&UserID=0 [accessed 30 April 2012].

10. Centre for Reviews and Dissemination, 2009. 'Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12009102367&UserID=0 [accessed 30 April 2012].

11. Centre for Reviews and Dissemination, 2011. 'Systematic review and meta-analysis of transurethral resection of the prostate versus minimally invasive procedures for the treatment of benign prostatic obstruction (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12010003874&UserID=0 [accessed 30 April 2012].

12. Centre for Reviews and Dissemination, 2003. 'Systematic review of minimally invasive techniques for relief of bladder outflow obstruction: update and re-appraisal (Structured abstract)'. Database of Abstracts of Reviews of Effects [internet]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12002008381&UserID=0 [accessed 30 April 2012].

13. Djavan B, Eckersberger E, Handl MJ, Brandner R, Sadri H,Lepor H, 2010. 'Durability and re-treatment rates of minimal invasive treatments of benign prostatic hyperplasia: a cross-analysis of the literature',*The Canadian Journal of Urology,* 17, 5249-5254.

14. Fayad AS, El Sheikh MG, Zakaria T, Elfottoh HA, Alsergany R, 2011. 'Holmium laser enucleation versus bipolar resection of the prostate: A prospective randomized study. Which to choose?', *Journal of Endourology*, 25, 1347-1352.

15. Gravas S, Bachmann A, Reich O, Roehrborn CG, Gilling PJ, De La Rosette J, 2011. 'Critical review of lasers in benign prostatic hyperplasia (BPH)', *BJU International*, 107, 1030-1043.

16. Kacker R & Williams SB, 2011. 'Endourologic procedures for benign prostatic hyperplasia: review of indications and outcomes', *Urology Journal*, 8, 171-176.

17. Krambeck AE, 2010. 'Evolution and success of holmium laser enucleation of the prostate', *Indian Journal of Urology*, 26, 404-409.

18. Kuntz RM, 2006. 'Current role of lasers in the treatment of benign prostatic hyperplasia (BPH)', *European Urology*, 49*,* 961-969.

19. Kuntz RM, 2007. 'Laser treatment of benign prostatic hyperplasia', *World Journal of Urology,* 25, 241-247.

20. Matlaga BR, Miller NL, Lingeman JE, 2007. 'Holmium laser treatment of benign prostatic hyperplasia: An update', *Current Opinion in Urology,* 17, 27-31.

21. McNicholas T & Kirby R, 2011. 'Benign prostatic hyperplasia and male lower urinary tract symptoms (LUTS)'. *Clinical Evidence.* Available from: http://bestpractice.bmj.com/best-practice/evidence/1801.html [accessed 30 April 2012].

22. Reich O, Gratzke C, Stief CG, 2006. 'Techniques and long-term results of surgical procedures for BPH', *European Urology,* 49, 970-978.

23. Seki N & Naito S, 2008. 'Holmium laser for benign prostatic hyperplasia', *Current Opinion in Urology,* 18, 41-45.

24. Seki N & Naito S, 2007. 'Instrumental treatments for benign prostatic obstruction', *Current Opinion in Urology,* 17, 17-21.

25. Son H, Song SH, Paick JS, 2010. 'Current laser treatments for benign prostatic hyperplasia', *Korean Journal of Urology,* 51,737-744.

26. Spatafora S, Conti G, Perachino M, Casarico A, Mazzi G, Pappagallo GL, 2007. 'Evidence-based guidelines for the management of lower urinary tract symptoms related to uncomplicated benign prostatic hyperplasia in Italy: Updated summary', *Current Medical Research and Opinion*, 23, 1715-1732.

27. Tzortzis V, Gravas S, de la Rosette JJMCH, 2009. 'Minimally invasive surgical treatments for benign prostatic hyperplasia', *European Urology, Supplements*, 8, 513-522.

Wrong patient group

28. Descazeaud A, Robert G, Azzousi AR, Ballereau C, Lukacs B, Haillot O et al, 2009. 'Laser treatment of benign prostatic hyperplasia in patients on oral anticoagulant therapy: A review', *BJU International*, 103, 1162-1165.

Wrong intervention

29. Hoekstra RJ, Van Melick HHE, Kok ET, Ruud Bosch JLH, 2010. 'A 10-year follow-up after transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia; Long-term results of a randomized controlled trial', *BJU International*, 106, 822-826.

30. Montorsi F & Moncada I, 2006. 'Safety and tolerability of treatment for BPH', *European Urology, Supplements*, 5, 1004-1012.

31. Razzaghi MR, Habibi G, Djavid GE, Gholamrezaee H, 2007. 'Laser prostatectomy versus transurethral resection of prostate in the treatment of benign prostatic hyperplasia'. *Saudi Medical Journal,* 28, 68-72.

Wrong outcomes

32. Briganti A, Naspro R, Gallina A, Salonia A, Vavassori I, Hurle R et al, 2006. 'Impact on sexual function of holmium laser enucleation versus transurethral resection of the prostate: Results of a prospective, 2-center, randomized trial', *Journal of Urology*, 175, 1817-1821.

33. Frieben RW, Lin HC, Hinh PP, Berardinelli F, Canfield SE, Wang R, 2010. 'The impact of minimally invasive surgeries for the treatment of symptomatic benign prostatic hyperplasia on male sexual function: A systematic review', *Asian Journal of Andrology*, 12, 500-508.

Not in English

34. Wu HZ, 2007. 'Application and development of all solid state green laser and photoselective vaporization of prostate', *Journal of Clinical Rehabilitative Tissue Engineering Research*, 11, 170-172.

Duplicates

35. Lourenco T, Pickard R, Vale L, Grant A, Fraser C, MacLennan G et al, 2008. 'Alternative approaches to endoscopic ablation for benign enlargement of the prostate: Systematic review of randomised controlled trials', *BMJ*, 337, 36-39.

36. Montorsi F, Naspro R, Salonia A, Suardi N, Briganti A, Zanoni M et al, 2008. 'Holmium laser enucleation versus transurethral resection of the prostate: Results from a 2-center prospective randomized trial in patients with obstructive benign prostatic hyperplasia'. *Journal of Urology*, 179, S87-S90.

37. Rigatti L, Naspro R, Salonia A, Centemero A, Ghezzi M, Guazzoni G et al, 2006. 'Urodynamics after TURP and HoLEP in urodynamically obstructed patients: Are there any differences at 1 year of follow-up?', *Urology*, 67, 1193-1198.

Additional HTAs and systematic reviews

38. Ahyai S & Lehrich K, 2007. 'Holmium laser enucleation versus transurethral resection of the prostate: 3-year follow-up results of a randomized clinical trial', *European Urology*, 52, 1456-63.

39. Berardinelli F, Hinh P, Wang R, 2009. 'Minimally invasive surgery in the management of benign prostatic hyperplasia', *Minerva Urologica e Nefrologica*, 61, 269-289.

40. Biester K, Skipka G, Jahn R, Buchberger B, Rohde V, Lange S, 2012. 'Systematic review of surgical treatments for benign prostatic hyperplasia and presentation of an approach to investigate therapeutic equivalence (non-inferiority)',*BJU International*, 109, 722-730.

41. Centre for Reviews and Dissemination, 2011. 'Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction (Structured abstract). Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=12007003746&UserID=0 [accessed 30 April 2012].

42. Herrmann TRW, Georgiou A, Bach T, Gross AJ, Oelke M, 2009. 'Laser treatments of the prostate vs. TURP/open prostatectomy: Systematic review of urodynamic data', *Minerva Urologica e Nefrologica,* 61, 309-324.

43. Medical Advisory Secretariat & Ontario Ministry of Health and Long-Term Care (MAS), 2006. 'Energy delivery systems for treatment of benign prostatic hyperplasia: an evidence-based analysis (Structured abstract)'. Health Technology Assessment Database [On-line]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=32006001045&UserID=0 [accessed 30 April 2012].

44. Obyn C & Mambourg F, 2008. Evaluation des certains nouveaux traitements du cancer de la prostate et de l'hypertrophie bénigne de la prostate: Ultrasons focalisés de haute densité (HIFU) pour le cancer de la prostate. Vaporisation photosélective de la prostate (PVP) et holmium laser pour l'hypertrophie bénigne de la prostate (Rep. No. KCE reports 89B (D/2008/10.273/62)), Bruxelles: Centre fédéral d'expertise des soins de santé (KCE). Available from: old.kce.fgov.be/Download.aspx?ID=1670 [accessed 30 April 2012].

45. Rieken M, Mundorff NE, Bonkat G, Wyler S, Bachmann A, 2010. 'Complications of laser prostatectomy: A review of recent data'. *World Journal of Urology*, 28, 53-62.

46. Tooher RL, 2011. 'Holmium laser prostatectomy for benign prostatic hyperplasia: a systematic review (Structured abstract)'. Health Technology Assessment Database [On-line]. Available from: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=32003000532&UserID=0 [accessed 30 April 2012].

Studies extracted in systemic reviews selected for updating in this report

47. Gupta N, Sivaramakrishna, Kumar R, Dogra PN, Seth A, 2006. 'Comparison of standard transurethral resection, transurethral vapour resection and holmium laser enucleation of the prostate for managing benign prostatic hyperplasia of >40 g', *BJU International*, 97, 85-89.

48. Wilson LC, Gilling PJ, Williams A, Kennett KM, Frampton CM, Westenberg AM et al, 2006. 'A randomised trial comparing holmium laser enucleation versus transurethral resection in the treatment of prostates larger than 40 grams: Results at 2 years', *European Urology*, 50, 569-573.

Appendix F Additional economic information

Summary of economic reviews identified

Author and date	Lourenco et al 2008
Title	Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
Type of economic evaluation	Cost-effectiveness analysis
Study objective	To assess the treatment option (or combination of options) that is the most cost-effective in treating BPH.
Interventions	TUMP, TUVP, KTP laser, TURP, HoLEP
Location/Setting	United Kingdom. The patient treatment setting was not specified although costs were calculated on the basis of a hospital inpatient setting.
Methods	Analytical approach: A Markov model was developed. The time horizon was 10 years, with individual cycle lengths of three months. Four health states were included in the model. Effectiveness data: Clinical effectiveness data were drawn from meta-analysis of published primary studies. Utility (QALY) data were imputed from studies exploring utility as a function of IPSS scores published by Kok et al (2002). Utility associated with procedural complications was mathematically 'mapped' to IPSS utility values. Cost data: Only costs incurred by the English NHS were considered. The price year was 2006 and the currency used was the UK pound sterling. A discount factor of 3.5% per annum was applied. Treatment sequences – guiding principles: Patients proceeded from treatment that was less to more invasive. Tissue ablative procedures (including HoLEP) would not be repeated. Minimally invasive procedures were not repeated more than once. TURP would only be repeated once and only after performing a pressure test. Never change to another treatment from the same category. Analysis of uncertainty: One-way sensitivity analysis was performed on eight variables used in the model. The authors commented that variation of these variables did not affect the set of non-dominated or non-extendedly dominated strategies. The impact of the sensitivity analysis on the decision to change treatment strategy was reported as being dependent on the function of willingness to pay for a QALY. In all but two cases however a change from base case treatment (defined as TURP with the option of a second TURP following initial treatment failure) would prove cost-effective.

Author and date	Stovsky et al 2006
Title	A clinical outcomes and cost analysis comparing photoselective vaporization of the prostate to alternative minimally invasive therapies and transurethral prostate resection for the treatment of benign prostatic hyperplasia.
Type of economic evaluation presented	Cost analysis
Study objective	To compare the clinical outcomes and costs of seven alternative procedural options for the treatment of BPH.
Interventions	PVP, ILC, TURP, TUNA, TUMT (TUMT was subdivided into three separate approaches).
Location/Setting	United States of America. It was assumed that: PVP procedures were performed in a hospital outpatient setting, TUNA and TUMT services were performed in a primary care setting, ILC was performed in a variety of settings including a freestanding ambulatory surgery centre and TURP procedures were performed in a hospital inpatient setting.
Methods	Analytical approach: A Markov model was developed. The time horizon was two years, with individual cycle lengths of one month. The study outlined eight adverse events associated with the procedural interventions including: incontinence, urinary tract infection, impotence/erectile dysfunction, dysuria/irritative voiding, bladder neck stenosis/stricture, urinary retention, hematuria and re-operation. Effectiveness data: The main outcomes of the model were average scores for AUASSI/I-PSS, QMAX and QOL. Clinical effectiveness data were drawn from meta-analysis of published primary studies. The methods used in the review were not thoroughly described and it is unclear how the utility (QOL) values were derived. Cost data: The costs included in the model included those associated with the initial intervention (which varied in setting), routine follow-up care related to BPH, the treatment of adverse events and procedural re-treatment. Only costs incurred by a third-party payer (US Medicare) were considered. The price year was 2005 and the currency used was US dollars. Despite the model incorporating costs across a two-year time horizon no discount factor was applied. Analysis of uncertainty: Several one-way sensitivity analyses were performed to test the robustness of the model results to different parameter values. A threshold analysis was used to determine the re-treatment rate at which the cost of PVP would be equal to that of TURP.

Author and date	Fraundorfer et al 2001
Title	Holmium laser resection of the prostate is more cost-effective than transurethral resection of the prostate: results of a randomized prospective study.
Type of economic evaluation presented	Cost minimisation analysis
Study objective	To conduct an analysis comparing the treatment costs of HoLRP to TURP.
Interventions	HoLRP and TURP
Location/Setting	New Zealand. All procedures were performed as hospital inpatient procedures.
Methods	Analytical approach: A cost-minimisation study was conducted using data collected from a randomised, single-centre, prospective study. Effectiveness data: The main effectiveness outcomes used in the model were: resection time (minutes), catheterisation time (hours), nursing contact time (minutes), hospital stay (hours), blood transfusion (n). The clinical outcomes presented were: urodynamic outcomes at six and 12 months (Qmax (mL/s), AUA score and Schafer grade. Questionnaires on quality of life and sexual/continence function were described to have been administered; however, the results of these were not detailed. Cost data: Only direct hospital costs were considered including: preoperative components, blood group and hold, operating room set-up/disposable and time, anaesthesia, recovery, catheter, fibre or loop, irrigation fluid, blood products, hospital stay, nursing extras, unplanned events in year 1, outpatient visits, operating suite, specific consumables, accommodation. Quantities and costs were not presented separately. All costs were presented in New Zealand dollars. The price year was not specified. Medical salary costs (urologist and anaesthesiologist) were not included. Analysis of uncertainty: No sensitivity analysis was performed.

Author and date	Salonia et al 2006
Title	Holmium laser enucleation versus open prostatectomy for benign prostatic hyperplasia: An inpatient cost analysis
Type of economic evaluation presented	Cost analysis
Study objective	To compare the cost of HoLEP compared to OP in the treatment of BPH for men with a large prostate.
Interventions	HoLEP and OP
Location/Setting	Italy. All procedures were performed as hospital inpatient procedures.
Methods	Analytical approach: A cost analysis was conducted using economic data collected from a randomised, single-centre, prospective clinical trial. Effectiveness data: Preoperative clinical data were presented; however, no postoperative clinical data were presented. Cost data: Only direct hospital costs were considered in the analysis. The costs used in the analysis included: premedication and prophylaxis, anaesthesia, OR surgical setup/disposables/fibres, irrigation fluid, autologous blood transfusion, homologous blood transfusion, OR time, postoperative holding area time, perioperative analgesic solution use, hospital stay, unplanned events. Quantities and costs were not presented separately. All costs were presented in both euros and US dollars although a currency conversion rate was not specified. The price year was not specified; however, as the trial took place between February and May 2004 it will be assumed that this was also the price year. Medical salary costs (urologist and anaesthesiologist) were not included. Analysis of uncertainty: No sensitivity analysis was performed.

Glossary and abbreviations

AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
ANZHSN	Australian and New Zealand Horizon Scanning Network
ARTG	Australian Register of Therapeutic Goods
AUA	American Urological Association
BNC	bladder-neck contracture
BPH	benign prostatic hyperplasia
CI	confidence interval
DAP	Decision Analytic Protocol
HESP	Health Expert Standing Panel
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
KTP	potassium titanyl phosphate
LUTS	lower urinary tract symptoms
MBS	Medical Benefits Schedule
MD	mean difference
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
OP	open prostatectomy

p	probability
PASC	Protocol Advisory Sub-Committee
PICO	population, intervention, comparator, outcomes
PVP	photoselective vaporisation of the prostate
PVR	post-void residual volume
QALY	quality-adjusted life year
Qmax	peak flow rate
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SR	systematic review
TGA	Therapeutic Goods Administration
TUIP	transurethral incisional prostatectomy
TUMT	transurethral microwave thermotherapy
TUNA	transurethral needle ablation
TUR	transurethral resection
TURP	transurethral resection of the prostate
VLAP	visual laser ablation of the prostate
YAG	yttrium, aluminium and garnet

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